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PATHOPHYSIOLOGY AND TREATMENT OF SUBARACHNOID HEMORRHAGE IN THE CYNOMOLGUS MONKEY

by

CHARLES SHELDON ROTHBERG

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled PATHOPHYSIOLOGY AND TREATMENT OF SUBARACHNOID HEMORRHAGE IN THE CYNOMOLGUS MONKEY submitted by CHARLES SHELDON ROTHBERG in partial fulfilment of the requirements for the degree of Doctor of Philosophy in EXPERIMENTAL SURGERY.

....

Bryce Weir

....

Co-Supervisors

Michael Grace

....

....

....

....

External Examiner

DATE April 2, 1979

TO MY FATHER . . . . . . WHOSE PRIDE AND FAITH IN ME NEVER CEASED.

ABSTRACT

In an experimental model using the cynomolgus monkey the pathophysiological responses to induced subarachnoid hemorrhage and the effectiveness of treatment of the subsequent cerebrovascular abnormalities were studied.

Using the intra-arterial 133 Xenon clearance technique for regional cerebral blood flow measurement, the reported work involves two major investigations. In the first, the pathophysiological responses to increasing volumes of subarachnoid blood were documented. Comparative studies of the acute effects of increasing volumes of subdural blood, and of subarachnoid injections of a large volume of artifical CSF were also performed.

The second major investigation concerned the effectiveness of the treatment combination of sodium nitroprusside and phenylephrine in improving cerebral blood flow, cerebrovascular resistance, cerebral vasospasm and neurological grade post-subarachnoid and post-subdural hemorrhage.

Subarachnoid hemorrhage caused a reduction in regional cerebral blood flow which was more marked and more persistent in the larger hemorrhage volume groups. During the immediate post-hemorrhage period (ca 2 1/2 hours) regional cerebral blood flow generally recovered in the lower hemorrhage volume groups, whereas in the larger volume

groups it remained low for the duration of the experiment.

Other significant experimental findings in the immediate post-hemorrhage period were: decreased cerebral perfusion pressure; increased cerebrovascular resistance; cerebral vasospasm, and elevated intracranial pressure. The larger hemorrhage volume groups showed a more marked and a longer duration of elevation of cerebrovascular resistance, and a longer duration of elevated intracranial pressure. Cerebral vasospasm was initially similar for these groups, but after 2 1/2 hours a better recovery of vessel caliber was demonstrated by the lower hemorrhage volume groups. Cerebral perfusion pressure recovered in all groups.

Following the insult in the subdural hemorrhage groups regional cerebral blood flow was unchanged for the lower volume group but decreased at the larger hemorrhage volume. Cerebral perfusion pressure was reduced in the immediate post-hemorrhage period but subsequently recovered for both groups. Cerebrovascular resistance was increased for the larger hemorrhage volume group but reduced for animals receiving the lower volume. Vasospasm was present in both groups in the post-insult period, and to the same degree as for corresponding volume subarachnoid hemorrhage groups. After 2 1/2 hours, vessel caliber recovery was more complete in the smaller volume subdural hemorrhage group than for the larger volume group. The magnitude of intracranial pressure elevation in these groups was also similar to that in the subarachnoid hemorrhage groups but was of shorter duration.

In the post-insult period for the group receiving artificial CSF there was a minimal reduction in regional cerebral blood flow, no change in cerebral perfusion pressure, and minimal increase in cerebrovascular resistance. No change in vessel caliber was found. Intracranial pressure elevation was similar to, but of shorter duration than that occurring in the subarachnoid and subdural hemorrhage groups.

Post-insult apnea was a finding common to all our experimental studies, the duration and frequency of which was greater in the larger subarachnoid hemorrhage volume groups.

In general, during the post-insult period, we found hypoxemia, hypocapnia and elevated alveolar-arterial oxygen differences which were more marked and of longer duration in the larger subarachnoid hemorrhage volume groups. The changes observed in arterial oxygenation were directly related to the duration of elevation of intracranial pressure and of right ventricular pressure. These findings generally correlated well with the pulmonary pathology, consisting of intra-alveolar and interstitial edema.

In general, those animals receiving large volumes of subarachnoid blood fared worse in all respects than animals in other groups.

In these investigations a total of six animals died acutely (within five hours of the intracranial insult) all with large subarachnoid hemorrhage volumes. These animals demonstrated decreases in regional cerebral blood flow, increases in cerebrovascular resistance, decreases in arterial oxygen and increases in alveolar-arterial oxygen difference of greater magnitude than the surviving animals. The degree of vasospasm was not different for the two subgroups.

In the second major investigation regional cerebral blood flow was significantly decreased following both subarachnoid and subdural hemorrhage insults. During the combination treatment regime of sodium nitroprusside and phenylephrine, administered post-hemorrhage, regional cerebral blood flow remained significantly reduced, cerebral perfusion pressure remained low, cerebrovascular resistance elevation was persistent and cerebral vasospasm unchanged. The post-insult cerebrovascular abnormalities were not different from those in the large hemorrhage volume untreated groups.

Following cessation of treatment, cerebral perfusion pressure recovered, regional cerebral blood flow remained significantly below control, cerebrovascular resistance was elevated and cerebral vasospasm was peristent. No difference in the neurological grade or survival was found between the same insult volume treated and untreated groups.

In the experimental group that was treated but did not receive an intracranial insult, regional cerebral blood flow and cerebral perfusion pressure were slightly diminished, cerebrovascular resistance was unchanged and no cerebral vessel spasm or vasodilation was observed. On completion of the therapy, both regional cerebral blood flow and cerebral perfusion pressure remained low, while cerebrovascular resistance and vessel caliber remained unchanged.

Our experimental findings suggest the following conclusions:

1. Subarachnoid hemorrhage is associated with reduced cerebral blood flow, elevated cerebrovasular resistance and cerebral vasospasm.
2. Subarachnoid hemorrhage impairs autoregulation.
3. The treatment regime of sodium nitroprusside and phenylephrine:
    (i) is ineffective in improving both post-subarachnoid hemorrhage and post-subdural hemorrhage reduced cerebral blood flow, elevated cerebrovascular resistance and cerebral vasospasm.
    (ii) impairs autoregulation
    (iii) can be toxic (lethal)
4. Cerebral vasospasm plays only a small part in the reduction of cerebral blood flow and elevation of cerebrovascular resistance, with the cerebral

microcirculation playing the major role.

5. Pulmonary pathology, giving rise to poor arterial oxygenation, and respiratory centre dysfunction evidenced by post-insult apnea and other respiratory pattern aberrations, are present in the period immediately following both subarachnoid and subdural hemorrhages. These pathophysiological responses are directly related to the duration of elevation of the intracranial pressure.
6. Morbidity and mortality from subarachnoid hemorrhage are, at least in part, related either singly or in combination to reduced cerebral perfusion, poor arterial oxygenation and respiratory centre dysfunction.

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CHAPTER I

INTRODUCTION

The surgical management of patients with ruptured intracranial aneurysms has markedly improved during the last decade with the introduction of the surgical microscope, microsurgical instrumentation and techniques, improved post-operative management in intensive care units, and various therapeutic agents in preventing rebleeding. However, at the present time, there is little that can be done to improve the deteriorated neurological status of those patients suffering a recent subarachnoid hemorrhage due to ruptured intracranial aneurysms (SAH(AR)). The present work is concerned with the pathophysiological responses to induced SAH in an experimental animal model. In particular, we are concerned with elucidation of the mechanisms responsible for the high morbidity and mortality resulting from SAH(AR). The present investigations are also directed towards possible treatment of reduced cerebral blood flow and cerebral vasospasm following subarachnoid hemorrhage, in an attempt to improve cerebral circulation and outcome from this disorder. If the poor neurological condition of patients with a recent aneurysmal rupture can be improved, then, in association with the improved neurosurgical techniques, survival will be markedly improved.

I. INCIDENCE, ETIOLOGY, MORBIDITY AND MORTALITY OF SUBARACHNOID HEMORRHAGE

The incidence of intracranial cerebral aneurysms in the population has been estimated, from various general autopsy series, to range from 2.1-7.6%(1,2,3,4). The occurrence of unruptured aneurysms in these series varied from 30% to more than 50%, however, in general, the majority of aneurysms found had ruptured.

Of all sudden and unexpected natural deaths 4-5% were due to spontaneous subarachnoid hemorrhage with the majority of these resulting from ruptured intracranial aneurysms (5,6,7). Pakarinen (8) reported that spontaneous subarachnoid hemorrhage accounted for 1.2% of all deaths during the period 1954-1961 in Helsinki, and of these , most were due to ruptured intracranial aneurysms. Others reported a somewhat smaller incidence of less than 1% (9,10).

The annual incidence of spontaneous subarachnoid hemorrhage has been reported by many investigators and ranges from 7-16.8 cases per 100,000 population (8,10,11,12). Intracranial cerebral aneurysms have been found to be the most common cause of spontaneous subarachnoid hemorrhage (5,8,13,14). McKissock and Paine (14), in their autopsy series of 237 cases of spontaneous subarachnoid hemorrhage, found 78% due to ruptured aneurysms, 7% due to arteriovenous malformation and 18% of undetermined etiology. In a review of the literature, Pakarinen (8) concluded that in general, the cause of spontaneous subarachnoid hemorrhage was a ruptured intracranial aneurysm in 69% of the cases studied angiographically, and in 77.2% of the cases at autopsy. In his own series, ruptured intracranial aneurysms were responsible for spontaneous subarachnoid hemorrhage in 67.9% of the cases at angiography and 82.4% at autopsy. The increase in incidence of cerebral aneurysms as the etiology found at autopsy in these studies is due to the relatively low mortality rate following subarachnoid hemorrhage due to arteriovenous malformations. The Cooperative Study on Intracranial Aneurysms and Subarachnoid Hemorrhage, consisting of 6368 cases of spontaneous subarachnoid hemorrhage during the period 1958-1965, reported the incidence of cerebral aneurysmal rupture to be 51% both at autopsy and angiography (15).

The overall mortality rate following an initial spontaneous subarachnoid hemorrhage is in the neighborhood of 25-50% (8,14,15), with approximately 50% of these dying within the first 24 hours (8,11,16). After this period of time the daily mortality rate gradually decreases (8,15,16). The majority of those patients dying (70%) had ruptured intracranial aneurysms (8). The Cooperative Study reports that of those patients dying within the first 72 hours following a spontaneous subarachnoid hemorrhage, 36% had ruptured intracranial aneurysms (15). This figure is lower than that reported by Pakarinen (8), most likely because the

Cooperative Study did not include those patients dying before hospital admission. Pakarinen (8) reported that 34% of patients dying from an initial spontaneous subarachnoid hemorrhage did not reach hospital.

The overall mortality rate from ruptured intracranial aneurysms due to the initial hemorrhage is approximately 50% (8,12,15,17). The majority of these, 50-93%, were dead within the first week (8,12,15,17). Pakarinen (8) reported that of those patients dying from an initial rupture within a week of the insult, 74% were dead within 24 hours.

The overall 24 hour mortality rate of initial intracranial aneurysmal rupture has been variously stated to range from 10-31.7% (8,15,17).

The mortality of patients with recurrent SAH(AR) is much higher than that of the initial bleed, and ranges from 33-64% of patients surviving the first bleed, and 64-76% of those with multiple recurrences (8,12,15,18,19,20). As with the initial hemorrhage, mortality is highest within the first week, especially the first 24 hours.

The incidence of ruptured intracranial aneurysms in the population is small, however, the mortality is high. The greatest mortality occurs during the first week following the bleed, and within this period, the greatest mortality occurs within the first 24 hours.

The factors responsible for acute morbidity and mortality following SAH(AR) include:

(i) intracerebral hematoma (15,21-26)
(ii) subdural hematoma (15,22,26)
(iii) intraventricular hemorrhage (22,23,27,28,29)
(iv) subarachnoid hematoma (23,26)
(v) cerebral ischemia and infarction (21,22,23,26,30)
(vi) brain swelling, edema and elevated intracranial pressure (31,32,33)
(vii) hydrocephalus (31,34,34(a)).

Space occupying lesions are frequent findings at autopsy for patients dying acutely from SAH(AR) (21-26,35). These lesions are considered as the immediate cause of death, since cerebral disruption (24), tentorial herniation and brainstem lesions (23,26,36) are found. Intracerebral hematomas are associated with ischemia and edematous changes which further aggravate the mass effect of the hematoma (23,35,37). Cyclic progression of these changes will lead to the patient's demise.

Clinical studies have demonstrated that death due to intracranial space occupying lesions results initially from respiratory paralysis (26,38,39).

Subarachnoid hematomas are found to be associated with death in SAH(AR) and these either act as space occupying lesions or compress the brainstem (26). Intraventricular hemorrhage (depending on the degree) is generally known to be associated with a universally unfavourable prognosis

(22,26,27,28,29).

Ischemia and infarction of cerebral tissue in patients dying acutely from ruptured intracranial aneurysms were generally not recognized as complications of this condition until demonstrated by Robertson in 1949 (24). Since that time, the presence of cerebral ischemia and infarction have been found in the majority of early deaths from ruptured intracranial aneurysms, either in association with mass lesions, or by themselves (21,22,23,24,26).

Ischemia and infarctive changes are considered important causes of the morbidity and mortality of this disorder (22,23,24,35). The various causes of ischemia and infarction following an aneurysmal rupture have been attributed to stretching and kinking of the cerebral vessels, as well as direct compression of the vessel lumen (23). Cerebral vasospasm following subarachnoid hemorrhage has been labelled a major cause of the cerebral ischemia and infarction found pathologically at autopsy (22,23,24,30,37,40,41). Cerebral vessel thrombosis has also been implicated in the development of ischemia and infarction (22,23,35).

Schneck (40) and Schneck and Kricheff (41) found, at autopsy studies of patients dying from subarachnoid hemorrhage due to aneurysmal rupture, that in up to 65% cerebral infarction was a dominant feature. These authors suggest that cerebral vasospasm by itself was not responsible for cerebral infarction, but may lead to ischemia, which in the presence of other factors, such as intracranial hypertension, systemic hypotension and associated space occupying lesions will result in infarction. The development of cerebral edema following aneurysmal rupture will also lead to a further compromised cerebral circulation (30).

The presence of subarachnoid hemorrhage alone (without its associated effects) has been found in 5-49% of autopsies of patients dying acutely from aneurysmal rupture depending on the particular series (15,24,26). Either ischemia and infarction were not evident, or a rapid increase in intracranial pressure occurred and caused respiratory paralysis and death.

Cerebral edema, brain swelling and attendant elevated intracranial pressure (ICP), depending on the degree, are associated with poor outcome following SAH(AR) (31,32,33). These changes give rise to both progressive cerebrovascular impairment (in cyclical fashion), as well as cerebral compression, resulting in patient deterioration. Efforts to reduce brain swelling and edema, as well as ICP, with hyperosmolar agents and steroids have met with some success as evidenced by improvement or stabilization of the patient's condition.

The development of acute hydrocephalus following SAH(AR) is well known, and may be associated with neurological deterioration (31,34,34(a)). The occurrence of hydrocephalus is believed to result from blockage of the CSF absorptive pathways. Cerebrospinal fluid drainage procedures in patients found to have hydrocephalus following SAH have been shown to result in clinical improvement (34,34(a)).

II. CEREBROVASCULAR DISTURBANCES FOLLOWING SUBARACHNOID HEMORRHAGE

Cerebral vasospasm frequently accompanies SAH(AR). The relationships between cerebral vasospasm and neurological grade, cerebral ischemia and infarction, and eventual outcome remains controversial. Correlation between spasm, grade and outcome following spontaneous intracranial aneurysmal rupture has been found by many clinical observers (42-56). Fergusson et al (57) commented that only a severe degree of cerebral vasospasm is associated with neurological deterioration. On the other hand, others have not found such a relationship between angiographically observed clinical vasospasm and neurological status and outcome (58-63). Millikan (58), in his comprehensive analytical review of 46 papers between the years 1938-1974 dealing with the clinical implications of cerebral vasospasm, did not find any firm evidence between spasm and neurological grade, outcome and brain pathology.

Postmortem examination of patients dying from spontaneous subarachnoid hemorrhage also yield conflicting results. Early investigators suggested that cerebral ischemia and infarction following aneurysmal rupture may be due to cerebral vasospasm (23,24). This relationship was found by Crompton (37). He noted that when cerebral infarction and vasospasm coincided, it was generally in the territory supplied by the constricted vessels. The findings of cerebral ischemia in the area of supply of the aneurysm bearing vessels suggests a role for vasospasm in the production of cerebral infarction (30,64). Wilkins et al (65) found that following subarachnoid hemorrhage, patients after 1-3 weeks demonstrated abnormal brain scans, presumably due to cerebral infarction in the distribution of the constricted cerebral vessels. Others however, (40,41) did not find any consistent relationship between infarction and spasm. They suggested that spasm may result in ischemia, but an association with other factors is needed for the development of cerebral infarction.

In general, experimental investigations of vasospasm subsequent to induced subarachnoid hemorrhage do not show a causal relationship between cerebrovascular spasm and neurological status and outcome (66-74). Landau et al (75) demonstrated in monkeys, following subarachnoid hemorrhage, that neurological deterioration correlated roughly with spasm in that, at times, both were present simultaneously. However, their overall general impression was that vasospasm did not correlate with neurological status.

Simeone et al (76) found that in monkeys, following an induced subarachnoid hemorrhage, severe vasospasm, at least to less than 50% of control diameters, was associated with poor neurological status and outcome. They suggested that the lack of this correlation in other studies was due to the presence of a milder degree of vasospasm insufficient to produce ischemia and associated neurological abnormalities. Heros et al (43) support this view.

Hashi et al (77) postulated that the poor neurological status 24-48 hours following subarachnoid hemorrhage in baboons was due to ischemia resulting from vasospasm and to compression of the smaller resistance vessels due to perivascular edema.

Postmortem cerebral pathology has not been found to correlate with experimentally induced cerebral vasospasm due to subarachnoid hemorrhage (76,78). These investigators did not find cerebral ischemia and infarction related to various degrees of vasospasm. Similarly, Fraser et al (79) demonstrated a poor correlation between cerebral vasospasm and perfusion defects using carbon black infusion following experimental subarachnoid hemorrhage in monkeys.

Cerebral blood flow measurements are now being performed more frequently in both clinical and experimental settings following subarachnoid hemorrhage. The general consensus is that cerebral blood flow is diminished following subarachnoid hemorrhage. Cerebral blood flow measurements aid in the clinical management of patients following aneurysmal rupture, viz. decisions regarding timing of aneurysm surgery (80) and are valuable prognostic indicators (70).

There have been many clinical studies demonstrating post-subarachnoid hemorrhage cerebral blood flow reduction that correlates both with the neurological grade and the eventual outcome (55,56,57,81-89). Several investigators have reported that reduced cerebral blood flow is associated with a poor neurological condition (59,80), while others have demonstrated that this reduction correlates with a poor eventual outcome (90,91,92). Some of these observers have also shown a direct relationship between cerebral vasospasm and reduced cerebral blood flow (55,56,57,82,83,86,87,89, 90,91,92). Others have not demonstrated such a relationship with reduced cerebral blood flow (55,57,59,61,62,80,84,88). Heilbrun et al (81) reported the global reduction in cerebral blood flow following subarachnoid hemorrhage in patients that was not correlated with vasospasm. However, they did state that some patients showed a focal cerebral blood flow reduction in the areas supplied by constricted vessels. Kutsuzawa et al (93) found a reduction in cerebral blood flow following subarachnoid hemorrhage that correlated with spasm, but not with varying degrees of neurological abnormalities, graded from mild to severe. Bergvall et al (62) demonstrated that reduced cerebral perfusion following subarachnoid hemorrhage was not correlated with either cerebral vasospasm or the eventual outcome.

It appears that there is general agreement that cerebral blood flow is diminised following subarachnoid hemorrhage due to aneurysmal rupture, and that this reduction is associated with poor neurological grade and outcome. Correlation between reduced cerebral blood flow and cerebral vasospasm remains controversial and unresolved.

Various experimental studies have demonstrated reductions in cerebral blood flow within 30-60 minutes of induction of the subarachnoid hemorrhage (67,70,74,76,78,94-99). Following this initial decrease, several investigators have demonstrated a tendancy for cerebral blood flow to recover to pre-insult levels (67,76,78,95,96,97) whereas others reported a persistent reduction in blood flow (70,74,76,78,95,96,99). A diminuition in cerebral blood flow immediately following subarachnoid hemorrhage has not been as consistently seen experimentally as it has clinically (98,99,100). Biphasic changes in cerebral blood flow following subarachnoid hemorrhage, consisting of an initial decrease, recovery, and then a gradual reduction, have also been seen (76,97). Some investigators have reported stability of cerebral blood flow following the hemorrhage with a resultant decrease 4-48 hrs later (99,100).

The involvement of cerebral vasospasm in the reduction of cerebral blood flow has been demonstrated by several of these authors (76,78,94,97,99,100). Others have noted the association of reduced cerebral blood flow and elevated intracranial pressure (96,98,99,100) with an associated decrease in cerebral perfusion pressure.

Lack of correlation of reduced cerebral blood flow and cerebral vasospasm has also been found experimentally (70,74,76,78,95). Asano (96) has suggested that spasm is involved with the reduction of cerebral blood flow, but that it is not the only factor. Reduced flow following subarachnoid hemorrhage has been found experimentally to be related to both neurological grade (74,95) and outcome (70,74,76,95,96).

Another cause of reduced cerebral blood flow following subarachnoid hemorrhage is impaired autoregulation. Experimental evidence of impaired autoregulation following a hemorrhage has been found in several studies (67,76,78,98, 99,100,101). Autoregulatory impairment has also been shown clinically (59,81,88).

Autoregulation is the mechanism by which cerebral blood flow maintains constancy despite changes in cerebral perfusion pressure (102). If this mechanism becomes defective, cerebral blood flow tends to passively follow the cerebral perfusion pressure (103). Thus, if the perfusion pressure is reduced, so is the cerebral flow (99).

Disturbed autoregulation is generally believed to arise from tissue hypoxia and acidosis resulting from ischemia

(59,81,104-108). Various investigators have reported that with the loss of autoregulation there is maximal vasodilation (104,109) arising from tissue ischemia and uncoupling of normal metabolic-circulatory control (99). Others (99), have postulated that ischemia and toxic agents disturb metabolism and disrupt autoregulatory control. The presence of hydrocephalus following subarachnoid hemorrhage has also been demonstrated to be associated with impaired autoregulation (59,81).

With disturbances of autoregulation, increases in intracranial pressure give rise to reduced cerebral blood flow (99). Following a subarachnoid hemorrhage, intracranial pressure has been found to be elevated both clinically (50,57,110) and experimentally (96,100,111-115) and results from subsequent cerebral edema (22,26,30,50,88,110,113,116), increased cerebral blood volume (55), blockage of CSF outflow pathways due to blood in the subarachnoid space (111,112,114) and intracranial hematoma (21,22,26,88,110). Elevated intracranial pressure alone, as well as following subarachnoid hemorrhage has been found to be associated with impaired autoregulation (117). Langfitt et al (117) have demonstrated that with marked intracranial pressure elevation there is loss of autoregulation which is persistent despite reduction of the intracranial pressure. Thus, with autoregulatory disturbances, and a decrease in cerebral perfusion pressure due to elevated intracranial pressure, cerebral blood flow will be diminished following subarachnoid hemorrhage if these factors are precipitated. There has been experimental evidence showing that if cerebral perfusion pressure falls below the lower autoregulatory limit (35-40 mmHg), in otherwise normal animals with increases in intracranial pressure, cerebral blood flow is reduced (102,103,118-122). It has also been demonstrated that cerebral blood flow may be diminished in cases with autoregulatory impairment and yet normal cerebral perfusion pressure (99).

Several investigators have considered disturbances in the microcirculation following subarachnoid hemorrhage. The poor correlation of cerebral vasospasm and reduced cerebral blood flow following subarachnoid hemorrhage has led many observers to postulate that the microcirculation is responsible for elevated cerebrovascular resistance and diminished cerebral blood flow (55,62,66,79,96,100,123). They stated that disturbances in the microcirculation were at least in part responsible for the post-subarachnoid hemorrhage diminuition in cerebral blood flow. Pathology found in the microcirculation after such an insult consists of periarteriolar and pericapillary edema, including astroglial, neuronal and endothelial swelling, as well as intravascular aggregation of red blood cells (96,100). These have been shown to result in capillary occlusion and non-filling (96). Other investigators using ischemic-anoxic models have demonstrated similar findings of perivascular edema, capillary occlusion and intravascular hemoconcentration and sludging (124-129). These changes result from ischemia and are believed to give rise to further reduction in cerebral blood flow and ischemia in cyclical fashion (96).

The duration of ischemia is related to the degree of microcirculatory disruption (126). The previously described pathological changes have been shown to be reversible if perfusion is restored within a certain period of time (96). Similarly, Tweed et al (130) in an ischemic rat model, demonstrated partial recovery of this "low-flow" state with systemic epinephrine. These findings have definite therapeutic implications for improving post-subarachnoid hemorrhage reduction in cerebral blood flow.

The association of reduced cerebral blood following subarachnoid hemorrhage with neurological grade, morbidity and mortality is widely accepted. As previously discussed, the correlation of cerebral vasospasm with reduced cerebral blood flow, neurological status and outcome is not as well established. Nevertheless, the majority of treatment regimes used for improving cerebral blood flow, neurological grade and quality of survival are directed at the relief of cerebral vasospasm.

An excellent review of cerebral vasospasm following subarachnoid hemorrhage has been recently published by Heros et al (43). Sundt et al (131) have reviewed the physiological mechanisms of importance in the control of cerebral blood flow. The mechanics of smooth muscle contraction and relaxation with respect to the cerebral vasculature have been reviewed by Sundt et al (131) and Norwood (132). The latter investigator has also reported on the possible sites of action of various spasmogenic agents involved with cerebral vasospasm (132).

III. TREATMENT OF CEREBROVASCULAR COMPLICATIONS FOLLOWING SUBARACHNOID HEMORRHAGE

In the light of the physiological mechanisms involved in smooth muscle relaxation, various pharmacological agents have been used to promote vascular relaxation and prevent spasm following subarachnoid hemorrhage. It is to be reconciled that vascular smooth muscle may be damaged by ischemia and become myonecrotic and may not respond to pharmacological vasodilator therapy (131,133,134). It is hoped that a period of grace exists during ischemia, prior to unresponsiveness, during which the therapeutic agents may be effective. The previously mentioned review articles (43,131,132) outline the current therapeutic regimes that are being investigated both clinically and experimentally.

Although the treatment regimes have a sound physiological basis, no consistent results have been demonstrated. Alpha adrenergic blocking agents including phentolamine and phenoxybenzamine, administered via various routes (IV, intracarotid, intrathecal) have shown some success in preventing spasm due to induced subarachnoid hemorrhage in experimental animals (135-142). Hashi et al (139) have also improved post-subarachnoid hemorrhage cerebral blood flow with alpha blocking agents. Other experimental studies have demonstrated no effect on vasospasm present following a subarachnoid hemorrhage (143). Martins et al (144) have reported a reduction in post-hemorrhage cerebral blood flow following intracisternal phentolamine. Clinical studies with these agents have in general not echoed the optimism reported by experimental observers (145,146). No improvements in post-SAH reduced cerebral blood flow, vasospasm, morbidity or mortality have been noted. However, Cummins et al (147) demonstrated improvement in the post-operative state of patients treated with intracarotid phenoxybenzamine when used as pretreatment as well as following clinical deterioration.

Beta adrenergic blockade with propanalol was not effective in improving the morbidity and mortality of patients following a spontaneous subarachnoid hemorrhage (145). Recently , naftidofuryl, a drug similar in structure to both local anesthetics and beta adrenergic blocking agents has been shown effective in increasing cerebral blood flow and decreasing cerebrovascular resistance in normal cats as well as in cats following a period of occlusive cerebral ischemia (148).

If given as pretreatment, isoproterenol, a beta adrenergic stimulating agent, was found to shorten the duration of vasospasm resulting from bathing cat basilar artery in blood (140). Wilkins (142) has demonstrated improvement in post-subarachnoid hemorrhage vasospasm with isoproterenol in experimental animals. Improvement in the neurological condition of post-aneurysmal rupture patients, deteriorating either pre or post-operatively due to vasospasm, has been demonstrated using a treatment combination of isoproterenol and lidocaine (149,150).

Phosphodiesterase inhibitors alone have not been effective in alleviating spasm either experimentally or clinically (142,151). However, treatment combinations of beta adrenergic stimulating agents (isoproterenol, salbutamol) and aminophylline, a phosphodiesterase inhibitor, have been found to alleviate vasospasm following induced subarachnoid hemorrhage in experimental animals (152,153). Similarly, this form of combination therapy has been reported to improve post-aneurysmal rupture vasospasm and neurological condition (154,155).

Pretreatments with serotonin blockers (kanamycin, reserpine, chlorpromazine, methylsergide) has been shown experimentally in vivo and in vitro to prevent the development of vasospasm due to subarachnoid hemorrhage and serotonin (156,157,158). Others have shown methylsergide to reverse serotonin induced spasm (159). Alpha adrenergic blockade (phenoxybenzamine) has been demonstrated to reverse in vivo, and block in vitro, serotonin induced vasospasm (141,158).

Prostaglandin E1 has been reported to improve cerebral blood flow, cerebral vasospasm and cerebrovascular resistance following subarachnoid hemorrhage in baboons (160), but no improvement in these parameters or clinical grade has been found following its administration in post-subarachnoid hemorrhage patients (161).

The status of prostaglandins in alleviating vasospasm and improving cerebral blood flow remains unsettled.

Exogenous cyclic AMP has been shown effective in experimental animals in attenuating cerebral vasospasm due to subarachnoid hemorrhage (162).

Smooth muscle relaxants have been used to combat the spasm and reduced cerebral blood flow following subarachnoid hemorrhage. Papaverine has been reported to improve vasospasm under these circumstances in experimental animals (163,164). Similarly, lidocaine has been found to improve post-subarachnoid hemorrhage spasm and blood flow in laboratory animals (165,166), and cerebral vasospasm in humans (165). Topical procainamide as well as chloramphenicol have been shown to relieve acute vasospasm, induced by basilar artery puncture, in the dog (167). The mechanisms of action of these agents remain elusive. Allen et al (168) have demonstrated relief of serotonin induced vasospasm in vitro. Allen (169) has also reported the effectiveness of the combination of sodium nitroprusside, a smooth muscle relaxant, and phenylephrine in improving post-operative neurological deterioration and vasospasm in subarachnoid hemorrhage patients. Heros et al (170) have shown relief of subarachnoid hemorrhage induced vasospasm in the dog by nitroprusside. Other investigators have reported reduction in cerebral blood flow following nitroprusside administration in experimental animals (171,172,173,174) and in patients (175). Griffiths et al (176), in humans, have noted reduction in cerebrovascular resistance and unchanged cerebral blood flow with nitroprusside. Others have observed the effectiveness of sodium nitroprusside in improving cerebral vasospasm, increased cerebrovascular resistance and reduced cerebral blood flow following both serotonin administration and induced subarachnoid hemorrhage in baboons (177).

Treatments other than those directed at the alleviation of vasospasm to improve cerebral blood flow have also been used. Hashi et al (139) demonstrated that administration of glycerol (a hyperosmolar agent) to reduce cerebral edema, resulted in only a temporary increase in cerebral blood flow and temporary decrease in cerebral vascular resistance following subarachnoid hemorrhage in baboons. Using hypertensive agents and blood volume expansion Kosnik et al (133) have reported improvements in post-operative deterioration of subarachnoid hemorrhage patients due to cerebral vasospasm. Brown et al (178(a)) demonstrated clinical improvement in patients with post-aneurysm clipping and post-SAH hemiplegia following dopamine-induced hypertension, mannitol and volume expansion. They believed that these improvements resulted from an increase in cerebral blood flow. van Dellen et al (178(b)) reported the prevention of cerebral infarction, and the clinical improvement in a patient, who developed ischemic signs following a Dandy trap procedure for a carotico-cavernous fistula, using metaraminol-induced systemic hypertension. They suggested this mode of therapy in the management of ischemic complications following aneurysm surgery. Boisvert et al (178(c)) showed improvement of regional cerebral blood flow and dilatation of the major cerebral arteries, following experimental SAH in rhesus monkeys, with metaraminol-induced systemic hypertension.

At this point in time however, no therapeutic regime has been shown to be definitely effective in improving post-SAH reduced CBF, cerebral vasospasm, morbidity and mortality. There is some enthusiasm about several of the aformentioned treatments, but as yet, their definitive roles have not been demonstrated.

IV. PULMONARY COMPLICATIONS WITH ELEVATED INTRACRANIAL PRESSURE

Pulmonary complications consisting of pulmonary vascular congestion, pulmonary edema, intra-alveolar hemorrhage and resultant ventilation-perfusion abnormalities have been observed in association with various intracranial disorders including cerebral trauma (178-186), cerebral neoplasms (187-188) and intracranial hemorrhage including subarachnoid hemorrhage (183,189,190,191). A common feature of these intracranial disorders is elevated intracranial pressure which occurs at some point in time during the insult (192). The pulmonary edema found in association with these disorders has been called "neurogenic pulmonary edema" (NPE) to distinguish it from other varieties of pulmonary edema and to emphasize the role played by the central nervous system in its pathogenesis (193).

This form of edema has been produced in experimental animals by cerebral trauma (194,195), hypothalamic lesions (179,196) and by both rapid elevation and high levels of intracranial pressure (197,198,199,200). The characteristics of neurogenic pulmonary edema and the possible mechanisms of its pathogenesis are discussed fully in 3 recent reviews articles (192,193,201). In general, it is believed that the centrally mediated massive sympathetic discharge subsequent to elevated intracranial pressure, in the face of normal hemodynamics and cardiac function, results in various changes in the pulmonary and systemic circulations resulting in pulmonary edema. Following the insult and in the presence of this form of pulmonary edema, cardiovascular hemodynamics and cardiac function have been found to be normal (193).

Resultant neurogenic pulmonary edema from various intracranial disorders has been shown to be associated with abnormal alveolar-arterial oxygen differences and with hypoxemia (180,182,191,202,203,204). Because of the known intracranial pressure elevations subsequent to subarachnoid hemorrhage, the development of pulmonary edema with subsequent hypoxemia is felt to further compromise the neurological status following subarachnoid hemorrhage.

The development of neurogenic pulmonary edema following intracranial pressure elevations both in patients and in experimental animals is widely accepted (180,182,185,202,203,205-210). This form of pulmonary edema with its associated hypoxemia has been suggested as one of the major causes of the poor survival of patients with head injuries (180,182,184,185,201,202,204,205), intracranial hemorrhage (189,191,210) and other types of intracranial pathology (203,209), as well of experimental animals with artificially elevated ICP (180,206).

Various abnormal breathing patterns including Cheyne-Stokes respiration, periodic respiration, irregular breathing, hyperventilation, Biot's respiration, sighing and gasping have been described following various intracranial disorders (cerebral trauma, intracranial hemorrhage, intracranial neoplasms) (182,201,205,211,212,213). These respiratory pattern abnormalities have been shown to result from injury and damage to the brain, especially the brainstem as well as the hemispheres (201,211,212,214,215). Patients developing abnormal respiratory patterns following intracranial insults have a poorer prognosis than those without abnormal breathing (182,205,211,212). Irregular breathing patterns tend to be more common in patients with lower levels of consciousness (211,212).

Death following experimental intracranial pressure elevation in laboratory animals has been shown to result initially from respiratory arrest followed by cardiovascular decompensation (38,216,217,218,219). Steiner et al (216) reported this same sequence of events subsequent to repeated subarachnoid hemorrhage in dogs. Respiratory failure, anticipating cardiac failure with the subsequent demise of patients with intracranial disorders and elevated intracranial pressure has been reported (39,220,221,222). Furthermore, this sequence of events, initiated by respiratory arrest, is frequently seen in neurosurgical units.

Thus, patients with brain damage from various intracranial disorders developing abnormal respiratory patterns may die from respiratory arrest because of the initial damage to the respiratory centre further insulted by low cerebral blood flow and hypoxemia from pulmonary edema.

V. UNANSWERED QUESTIONS

While much is now known about the sequelae of SAH, a number of important questions still remain:

1) What are the factors responsible for the morbidity and mortality following SAH?
2) What are the pathophysiological changes during the hemorrhage, and what role do they play in determining the final outcome?
3) What factors are responsible for the reduction of cerebral blood flow following SAH? Is visualized cerebral vasospasm involved? Do disturbances in the cerebral microcirculation play a role?
4) How are post-SAH cerebral blood flow changes related to neurological grade and outcome?
5) Are the respiratory centres injured as a result of SAH? What role do they play in the quality of survival following SAH?
6) Does pulmonary pathology (NPE) occur as a consequence of SAH? Is it involved in the poor outcome of this disorder?

Concerning the therapy of neurological deterioration following SAH, much has been tried, but the results remain poor. There has been a great deal of activity in this field, and many agents have been utilized, but no effective therapy has yet been found. The problem remains that we do not know enough about the pathophysiological changes that result subsequent to SAH. Therapies known to be effective under other circumstances have not been found to be efficacious in SAH, possibly because of the disrupted physiological mechanisms, of which we know very little.

VI. THE PRESENT STUDY

The present study is specifically directed to provide answers to the posed questions concerning the pathophysiological mechanisms responsible for the morbidity and mortality following SAH. In this study, we also tested the efficacity of a treatment regime in improving post-SAH reduced CBF, vasospasm and survival.

An experimental model, using the cynomolgus monkey, has been developed during several years in this laboratory and this model is used for the reported studies. The experimental study that was undertaken has 2 principal component investigations. The first component is directed towards studying the pathophysiological responses, as well as the degree of response, to increasing volumes of subarachnoid blood. In this first investigation, we also studied the responses to large volumes of injected subdural blood as well as to a large volume of subarachnoid artificial CSF.

The second component is concerned with determining the effectiveness of the treatment combination of sodium nitroprusside and phenylephrine in improving post-SAH reduced cerebral blood flow, increased cerebrovascular resistance, cerebral vasospasm and survival. In this study, we also investigated the effectiveness of this treatment program in improving the aforementioned parameters in animals receiving a subdural hemorrhage.

The physiological effects of sodium nitroprusside and phenylephrine in our experimental model were studied in a third group of animals not receiving an intracranial insult.

The experimental model, experimental design, instrumentation and methodology for both of these major investigations are described in detail in the following chapter, Chapter II Methods.

The results of both studies, contrasts and comparisons of the various groups, statistical significance of the findings and correlations are compiled and fully presented in Chapter III Results.

CHAPTER II

MATERIALS AND METHODS

A general description of the experimental techniques and procedures followed in this investigative study and a detailed experimental design is presented below. Many of the techniques described are unchanged throughout the course of the present study. However, several variations of the basic experimental procedures were used and these are specifically described where appropriate.

The first study to be described (Study A) was an investigation of the pathophysiological responses to induced SAH in the spontaneously breathing primate. The second study (Study B) examined the effectiveness of treatment, with administration of simultaneous sodium nitroprusside and phenylephrine, in improving the rCBF reduction subsequent to induced SAH and SDH.

I. ANIMAL PREPARATION

Juvenile and adult female cynomolgus (Macaca irus) monkeys weighing between 2.2 and 4.3 kg were utilized. Anesthesia was induced and maintained with intramuscular phencyclidine hydrochloride (Sernylan(R) - Bio-ceutic Laboratories) 3 mg/kg. Sernylan(R) acts principally on the central nervous system (223). It does not have any significant effect on CBF (224,225). Blood pressure and respiration are in general not altered by this drug

(223,226); minimal elevations in blood pressure of short duration have, however, been reported (223,226). With Sernylan(R), the time to immobilization of the animal is 8-12 minutes, and duration of action is 60-240 minutes (227). In our experiments, Sernylan(R) was generally administered only once, and by the time the CBF determination prior to the intracranial insult was performed, the peak effect of the drug had already passed. Thus, the possibility of any untoward effects of the drug on CBF and blood pressure in our data at this point onward would be eliminated.

The Sernylan(R) was administered to the animal at the vivarium prior to transportation to the laboratory. The initial experimental procedure was to introduce an endotracheal tube, and subsequently the animals were allowed to breathe spontaneously on a mixture 2:1 nitrous oxide (N20) and oxygen (02) at a rate of 3 L/min. Anesthesia was maintained during the experimental studies by both phencyclidine and N20. There are conflicting reports concerning the effect of N20 on CBF and intracranial pressure. At present, the general consensus is that N20 causes very minimal, if any changes at all in CBF and intracranial pressure (228,229,230,231).

For most animals, as mentioned, Sernylan(R) was given only once, prior to the experiment; a few animals had supplementary Sernylan anesthesia at one-half the original 3 mg/kg dose. These latter animals (in the SAH volume series) received the smaller SAH volumes (1.0 and 1.33 ml/kg) and they showed signs of arousal in the later stages of the experiment.

Body temperature was continuously monitored with an esophageal thermometer (Tele-Thermometer-Yellow Springs Instrument Co.) and maintained between 36° and 38°C with a small heating pad underneath the animals. Standard-limb-lead electrocardiography was utilized in Study A (Beckman Dynograph (Type R) Recorder) and in Study B (Sanborn Company ECG Recorder, Model 51).

Respiratory rate and tidal volume were recorded using a Vertek pneumotachograph (Hewlett Packard, HP Vertek Series 4000 VR, HP model 47303A) attached directly to the endotracheal tube.

II. SURGICAL PREPARATION

Femoral artery catheterization was performed and the catheter was passed up to the mid-thoracic aorta level. Arterial blood samples were immediately obtained for blood gas analysis and pH determination. (Instrument Laboratory Inc., pH/Gas Analyzer, model 113). In most cases a flow of 1 L/min O2 and 2 L/min N2O was adequate to keep the pre-insult arterial oxygen partial pressure (PaO2) within the physiological range. In those cases in which PaO2 was not within normal physiological limits the O2 flow was appropriately adjusted and the breathing mixture remained fixed for the duration of the study. PIO2, the inspired O2 partial pressure, was also recorded. The alveolar O2, PAO2, was calculated from the arterial carbon dioxide partial pressure (PaCO2) and PIO2 values, viz.

$$PAO2 = PIO2 - \frac{PaCO2}{0.8}$$

The alveolar-arterial oxygen difference (A-aDO2) was calculated as PAO2 - PaO2.

Arterial blood gases and pH were measured for alternate flows in the pre-SAH period for the 4 volume groups if the respiratory parameters, Vt and RR were stable and comparable to those at the previous flow, and if the blood gases were within normal limits. If not, the analysis was repeated. In the other experimental groups,pH, PaCO2 and PaO2 analyses were made during each pre-insult flow. Blood gas analysis and pH determination were performed for each CBF determination post-insult in all groups.

Hematocrit determinations, required for rCBF calculation, were carried out on average 4 times during each experiment; 2 determinations pre-SAH and 2 post-SAH, the final 1 at the completion of the experiment.

The mean arterial blood pressure (MaBP) was continuously measured using a pressure transducer (Statham P23dB) connected to the femoral artery catheter.

A burr hole, with 2 opposing offsets 2 mm deep and 2 mm wide drilled into the adjacent bone, was made in the right mid-parietal area to accommodate the intracranial pressure (ICP) device (a modification of the ICP device described by de Rougemont (232)). This device was connected to a Statham P23dB pressure transducer with a hydrostatic column, and the pressures graphically recorded.

The systolic right ventricular pressure was measured throughout Study B and for the artificial CSF group in Study A via a femoral vein catheter placed in the right ventricle and connected to a Statham P23dB pressure transducer. The positioning of this catheter was verified by the recording of large systolic waves from the right ventricle and also on postmortem examination of those animals dying during the experiment.

All pressure transducers were calibrated prior to, and at the termination of each experiment, using a mercury manometer. Zero drift on the chart recorder was frequently checked during the experiment and adjusted as required.

Fluid balance was maintained by intravenous administration of a solution of normal saline via a peripheral vein. In Study B, the drugs were administered in 5% D/W via a peripheral arm vein. The fluids were administered at a constant rate using an IVAC 500 (IVAC (R) Corporation) infusion pump.

For all animals receiving an intracranial injection a midline cranial twist drill hole was made (1.5 mm in diameter), 0.5 to 1.0 cm dorsal to the nasion, through which the needle for hemorrhage induction and artificial CSF injection was passed. Hemostasis was maintained by cauterization and bone wax application, and the defect was sealed until the time of the insult.

Cervical dissection to the common carotid artery bifurcation was performed with the aid of an operating microscope (Codman Mark II). The cervical portion of the common carotid artery was exposed and a 7-0 silk purse-string was placed in the wall of this vessel approximately 2 cm proximal to the bifurcation. The diameter of the purse-string was approximately 1 mm. Subsequently, the external carotid artery was clipped at its origin using a modified Heifitz aneurysm clip. A 20-gauge catheter (Medicut) was then inserted, through the purse-string, into the common carotid and passed up to the origin of the internal carotid artery. This catheter was then coupled to a 16-guage catheter which was connected to an automatic injector system using a 3-way stopcock assembly (fig. 1). At the completion of the experimental studies the carotid catheter was removed and the purse-string tightened to close the arteriotomy.

III. METHOD OF SIMULATING SUBARACHNOID HEMORRHAGE

This technique was initially described by Weir et al (71) in this laboratory. We have modified this slightly as described. A specially designed 19-gauge spinal needle, with a circumferentially bevelled tip and two side holes, was inserted through the midline frontal twist drill hole and advanced, with fluoroscopic control, along the floor of the anterior fossa. The needle tip was advanced to the tuberculum sella and then 3 mm beyond this. Previous studies had revealed, at this position, that the side holes are in the chiasmatic cistern. The needle was then secured to the skull by a screw device through which the needle passes. Figure 2 illustrates the positioning of the needle.

In Study A, 4 different SAH volumes of fresh autogenous blood were used 1.0,1.33, 1.67 and 2.0 ml/kg of body weight. The SAH was induced by manual injection at a rate of 1 ml/5 sec. The ICP level was determined by the volume of injectate and the rate of injection; it was kept at least 10-20 mm Hg below the MaBP. If, during the SAH induction, the ICP rose to a level close to the MaBP, the injection rate was slowed so as to keep the ICP within the specified range. The identical technique was used for the artificial CSF group in Study A and the SAH group in Study B. The artificial CSF injected was Elliott's "B" solution, and was prepared as described by Elliott et al (232(a)). The fluid was injected at normal pH (7.35) and temperature (37°C).

The subdural hemorrhage (SDH) series of studies A and B were performed in a similar manner but the injection was made into the prechiasmatic subdural space. In these latter groups the side holes of the injection needle were not in the chiasmatic cistern, but rather in front of it in the prechiasmatic subdural space.

IV. HANDLING AND DISPENSING OF 133 XENON

Cerebral blood flow was measured by the intra-arterial 133 Xenon clearance method of Lassen et al (233). 133 Xenon gas is relatively inexpensive and chemically inert and has a physical half-life of 5.3 days. The 133 Xenon gas is obtained from ORNL (Oak Ridge National Laboratory) in 1 Curie quantities contained in glass, break-seal vials. Since an aqueous solution of 133 Xenon is required for intra-arterial rCBF determinations, a special handling and dispensing system with high transfer/recovery efficiency (nearly 99%) was constructed in this laboratory (234). For the rCBF studies approximately 50-60 mCi 133 Xenon dissolved in 5 ml. saline was dispensed into an glass syringe, and then transferred into an automatic injector system.

V. ADMINISTRATION AND DETECTION OF 133 XENON

An automatic injector device which was utilized to inject 2.5-3.5 mCi in approximately 0.3 ml of 133 Xenon into the internal carotid artery (235) is shown in figure 2. The

133 Xenon injection was immediately followed by an 0.8 ml heparinized saline flush. The 133 Xenon was delivered in 1.2 seconds and the saline flush in 2.7 seconds.

The regional clearance rates for 133 Xenon from the brain tissue were measured using a 6-detector scintillation counter assembly constructed in this laboratory (fig. 3). The regional volumes of the brain "viewed" by the detectors were frontal, parietal, parieto-occipital and temporal (detectors 1,2,3 and 5 respectively). Detectors 4 and 6 recorded radioactivity from the orbital and cerebellar regions respectively. The orbital probe acted as a control. Figure 4 shows the relative positions of the 6 detectors. The group of 6 detectors was placed on the left side of the head (ipsilateral to the side of the injection). Each scintillation counter comprised a 0.60 cm diameter, 1.25 cm thick sodium iodide thallium activated crystal (NaI(Tl)) coupled to a 1.25 cm diameter photomultiplier (Phillips XP 101) with a truncated plexiglass light guide. The detectors, spaced at a distance of 1 cm from each other, were mounted in a stainless steel collimator block with the front face of each crystal recessed 7.5 cm from the block face. An additional 1.5 cm thick lead collimator applied to the block face ensured measurement of radioactivity from discrete volumes of brain tissue. A schematic diagram of the 6 detector system is shown in figure 5. The isoresponse (i.e. isocounting) curves for 2 adjacent detectors are shown in figure 6. Radioactivity was also measured from the contralateral side using a scintillation counter with a 2.54 cm diameter and 1.27 cm thick NaI(Tl) crystal. This detector was collimated by a cylindrical lead tube 11 cm long and 1.5 cm thick. The isoresponse curves for this collimator detector was measured with a point source of 133 Xenon in water and is shown in figure 7. The multidetector system viewed regional volumes of the brain, whereas this large detector gave us an overall view of the brain.

Pulses from each detector were sorted via a preamplifier and an amplifier and input into single channel analyzers which accepted pulses equivalent to the energy range 70 to 90 Kev. The output (sampling time of 2 seconds) from each single channel analyzer (SCA) was fed into the data acquisition system. Visual display of the 133 Xenon clearance rates from each brain region was provided by a small monitor in the laboratory. Data acquisition and retrieval was accomplished via a control teletype also located in the laboratory. The radioisotope clearance curves were analyzed by an on-line digital computer (HP 2100). Figure 8 shows the general instrumentation in our laboratory.

For an experimental measurement, background radiation (remaining activity) was recorded for a 2 minute period and a calculated mean value was subtracted from the clearance curves prior to the computer calculation of cerebral blood flow values.

Correct placement of the multidetector system was achieved by applying a plastic template (with 6 radiopaque rings representing the detectors) to the left lateral surface of the skull. Manipulation of the monkey's head relative to the position of the template with fluorscopy ensured reproducible positioning of the detectors relative to the brain (fig. 9).

Mean regional cerebral blood flow was determined by averaging measured flow values (rCBF) from the 4 supratentorially placed detectors (probes 1,2,3 and 5). Global, or general hemispheric cerebral blood flow was determined from the contralateral detector.

VI. CALCULATION OF CEREBRAL BLOOD FLOW

Cerebral blood flow values were calculated by biexponential (compartmental), stochastic (height/area (H/A)) and initial-slope-index (ISI) methods. A detailed discussion of these 3 methods of CBF calculation has been presented elsewhere (223,236) and will only be briefly reviewed here.

In the compartmental method of analysis, it is assumed that a semilogarithmic replot of the clearance curve of 133 Xenon can be assumed as 2 exponential components. From these 2 clearance phases, blood flow in the grey (fg) and white (fw) matter can be determined from the zero time intercepts of the 2 lines. Knowing the perfusion rates and the relative weights of each tissue, the weighted mean of blood flow for the cerebral tissue under observation can be calculated as follows:

$$\overline{fc} = Wg.fg + Ww.fw \text{ ml/100gm/min}$$

where $\overline{fc}$ is mean compartmental blood flow and the relative weights of the grey and white matter are represented by Wg and Ww respectively.

The stochastic or H/A method formulated mathematically by Zierler (237) can be applied to calculate the mean flow values from the clearance according to the equation:

$$\text{rCBF} = \frac{\text{Ho-H10}}{\text{A10-Background}} .\lambda.100\text{ml/100gm/min}$$

where Ho corresponds to the total number of particles (radioactivity) to be cleared and H10 the level of the clearance curve at 10 minutes. The area under the clearance curve between zero time and 10 minutes is denoted by A10 and is determined by integrating the counts recorded during the 10 minute interval. The mean tissue:blood solubility coefficient for 133 Xenon is represented as λ.

The initial-slope-index (ISI) method utilizes the calculated slope of the first 1.5 to 2.0 minutes of the logarithmic clearance curve. An estimate of the mean CBF can be readily determined using:

$$\text{rCBF(ISI)} = 100(\lambda g)(2.30 \text{ D initial}) \text{ ml/100gm/min.}$$

where λg corresponds to the 133 Xenon partition coefficient of grey matter and D represents the numerical value of the slope of the clearance curves.

Arterial carbon dioxide levels have a profound influence on CBF, and since the animals in these studies were allowed to breathe spontaneously, PaCO2 fluctuations were possible. Flow values corrected for PaCO2 and also uncorrected values have been calculated; the corrected values were adjusted to a standard PaCO2 of 40 mmHg. It has been shown (238) that for every mm Hg change in PaCO2 there is a 2.5% change in CBF in the same direction; this degree of adjustment was incorporated in the computer program. In the present studies all animals were allowed to breathe spontaneously and marked changes in respiratory pattern and in PaCO2 levels were found subsequent to the insult. We reasoned that after the insult, the responsiveness of the cerebral vessels may be variable and not predictable. It was therefore felt that correcting the CBF values for PaCO2 in our experiments would be of questionable value and would most likely lead to erroneous results. This has been pointed out by Bruce et al (239). Thus, all CBF data and results reported are uncorrected unless otherwise stated.

The partition coefficient for 133 Xenon in the grey and white matter was calculated according to the method of Veall and Mallett (240) using the solubilities of 133 Xenon in grey and white matter of baboons (241). Since hematocrit influences the solubility coefficient of 133 Xenon in whole blood and the blood-brain partition coefficient, a correction described by Veall and Mallett (240) was incorporated into the CBF calculation. A mean partition coefficient for the brain was calculated on the basis of a 52:48, grey : white matter ratio as determined for the baboon brain by James et al (241).

The calculation of CBF presupposes that the recorded clearance curve represents a single transit of the tracer and that the tracer does not recirculate to the counting field. Even though the lungs function as a very effective filter for inert gases with low solubility (90% of 133 Xenon is cleared during the first passage through the lungs and the remaining 10% is distributed in the total cardiac output with only 14% of the recirculating activity distributed to the brain) recirculation does occur. However, only in the presence of gross pulmonary insufficiency or with a rebreathing ventilation system does recirculation become a significant factor in CBF determination (238). In our experiments, exhaled 133 Xenon was removed by a hose to the atmosphere outside the building. Correction for recirculation was not performed.

VII. CEREBROVASCULAR RESISTANCE

The cerebrovascular resistance (CVR) was calculated from the formula:

$$\text{Cerebrovascular Resistance} = \frac{\text{Cerebral Perfusion Pressure}}{\text{Cerebral Blood Flow}} \quad (102)$$

$$\text{CVR} = \frac{\text{CPP (mmHg)}}{\text{CBF (ml/100gm/min)}}$$

Throughout this manuscript the calculated CVR will be designated as the CVR index, obviating the need to repeat the resistance units.

VIII. ANGIOGRAPHICAL STUDIES

Cerebral angiography was performed in all experimental studies by a manual injection of 1.5 ml Meglumine iothalamate (Conray 60) into the common carotid artery catheter. Only lateral cerebral angiograms were obtained and care was taken to maintain a constant magnification factor during each experiment.

Only those angiograms showing the arterial phase most distinctly were selected for vessel diameter measurement purposes. Only the large intradural capacitance vessels were measured; intradural internal carotid artery (IDICA) above and below the origin of the posterior communicating artery (C1,C2), middle cerebral artery (MCA) and the proximal pericallosal artery (CA). These measurement sites are shown schematically in figure 10 and on the cerebral angiogram in figure 11.

Arterial (intra-luminal) calibers at these predetermined fixed locations were measured with an optical micrometer lens system (Nikon, Nippon, Kogaku K,K, Tokyo, Japan). Two films, 2 to 3 minutes apart were obtained for each angiography study, and the vessels shown on each film were measured at the predetermined sites. The mean diameter value for each artery obtained from the readings of the 2 films was calculated and used in the statistical analysis.

IX. MEASUREMENT OF INTRACRANIAL PRESSURE

The ICP was measured using an intracranial, extradural self-locking membrane device system as shown in figure (12). This system is a development of the one described by de Rougement et al (232), and attains to the "coplanar principle" discussed by MacKay (242). The unit consists of a bell shaped chamber which is filled with saline and connected, via a hydrostatic column, to a Statham P23Db pressure transducer. The membrane is secured at the wide end and is flush with the surface. The device is inserted into a mid-parietal burr hole with side extensions to accommodate the 2 wings, it is then rotated 45° to secure these appendages under the bone; the locking nut secures the unit to the skull. The rubber membrane, as shown, is coplanar with the dura, and an "O" ring seals the defect between the bone edges and the device, supplemented with RTU adhesive to ensure an air tight coupling.

The response of this pressure measurement system is linear from zero to 300 mm Hg and it is unaffected by small (i.e. physiologic) temperature changes.

Prior to its insertion into the skull, the ICP monitor was calibrated to zero at atmospheric pressure. This system allowed continuous ICP monitoring and also instantaneous measurement of the ICP during the induction and after the hemorrhage. Immediately before SAH induction the ICP zero points were checked and the appropriate adjustments made if necessary. Further checks and adjustments were made during the experimental period. At the termination of each experiment the zero points were again checked, and any changes noted were corrected for in the ICP calculation.

X. CALCULATION OF CEREBRAL PERFUSION PRESSURE

The cerebral perfusion pressure (CPP) was calculated as,

Cerebral Perfusion Pressure=Mean Arterial Blood Pressure-Intracranial Pressure

$$\text{CPP(mmHg)} = \text{MaBP(mmHg)} - \text{ICP(mmHg)} \qquad (243)$$

More accurately CPP is the difference between the MaBP and the mean ICP plus the mean cerebral venous pressure (mCVP):

CPP = MaBP - (mICP+mCVP) (66)

However, CVP was not measured in our studies but, we believe CPP calculated as MaBP minus ICP to be an adequate and accurate reflection of the CPP, since the CVP under normal conditions is approximately 5 mm Hg (66) and contributes little to the CPP. The accuracy of this definition of CPP under normal and near normal circumstances has been supported by others (243,244). In the present studies pathological changes did occur and possibly caused changes in cerebral blood volume, such as have been reported by Grubb et al (55,245), which may have influenced CVP.

XI. NEUROLOGICAL ASSESSMENT

Neurological assessment was made for all animals surviving at 5 hours, and again for the survivors at 20 hours post-insult. A 5 division grading system was utilized in the neurological examination.

Grade 1: Alert, active, vocal, neurologically normal, accepts food and water, aggressive.

Grade 2: lethargic, somnolent, attempts to get up, sitting or standing but unsteady and with poor balance.

Grade 3: No spontaneous attempts to become upright, responds to stimulation appropriately (visual, auditory, tactile, painful).

Grade 4: Obtunded, no response to stimulation of any form, remains inactive.

Grade 5: Moribund, totally unresponsive, failing vital signs.

XII. ELECTRON MICROSCOPY STUDIES

Fixation of monkey cerebral vessels was performed by intracardiac and intracarotid infusion with Krebs-Ringer solution contianing 4% glutaraldehyde in Millonig's phosphate buffer. Twenty monkeys were perfused in this manner, 13 of which were of Study A and 7 belonged to Study B. After perfusion for approximately 15 minutes (500-600 ml of glutaraldehyde) the brain was removed. The vessels examined in this fashion were the IDICA, MCA, CA, distal pericallosal artery (DPA), basilar artery (BA), internal carotid artery in the neck, and the vertebral arteries (VA). For illustrative and descriptive purposes in this study, only the IDICA, MCA, CA and DPA vessels are used. The IDICA, MCA and CA segments corresponded to the sites used for angiographic demonstration and measurement of vessel caliber.

All samples were placed in small vials containing the perfusion fixative immediately upon removal from the brain. Tissues were postfixed in 1% osmium tetroxide solution, dehydrated with ethanol and embedded in Epon. After staining, section were viewed with a JEM-7A electron microscope.

XIII. POSTMORTEM EXAMINATION

On removal of the ICP device either pre or postmortem, the state of the intracranial contents was assessed by palpation of the dura through the burr hole. The dura was graded as normal, slightly full, full or tight. At postmortem the brains of all animals were removed and examined grossly, and graded as normal, slightly swollen, swollen or bulging on both observation and palpation. They were then weighed and photographed, and subsequently placed in 10% formaldehyde solution. The brains perfused with glutaraldehyde were not weighed and thus not included when brain weight comparisons were made for the different groups. Following at least a 2 week period in formaldehyde the brains were re-weighed and then cut into thick slices for gross pathological examination and photography. This thick sectioning procedure for pathology and photography was also followed for the glutaraldehyde perfused brains.

The brains of 3 animals in Study A were submitted for histological examination. Because of the expense, and also the time required for histological studies it was not possible to perform these examinations for a significant fraction of the animals in this investigation, although this possibility exists for the future.

The lungs of all animals in Study B and in the artificial CSF group of Study A were removed at postmortem. For those animals not perfused with glutaraldehyde the lungs were removed as a unit with the tracheobronchial tree and were examined and weighed. They were then inflated through the trachea with 10% formaldehyde and the tracheobronchial tree tied off to retain the formaldehyde in the lungs. The lungs were then immersed in a 10% formaldehyde solution for a period of at least 2-3 weeks. After this perrod of time, the lungs were sectioned, stained and examined histologically. The lungs of the glutaraldehyde perfused animals were examined in situ; blocks of lung tissue were removed and stored in 10% formaldehyde solution for a 2 week period before sectioning and staining for histological examination.

XIV. EXPERIMENTAL STUDIES

OBJECTIVES AND DESIGN

Two major experimental investigations were carried out. The first study was involved with the delineation of the pathophysiological responses to induced SAH and SDH, and the second with the treatment of reduced rCBF subsequent to the insult. Each of these major studies comprised 3 substudies.

This section is concerned with the detailed objectives for each of the substudies in the 2 major investigations and with the experimental design. For all the substudies making up the first major investigation the experimental design is the same. In the second major study the experimental design varies somewhat from the first study, and also, there are slight variations in the design of the individual substudies.

The basic design of the experimental investigations will be fully described in the following with particular reference to the first substudy of the first major investigation. Variations in experimental design from this basic theme will be discussed with respect to the particular substudy to which it refers.

A. STUDY A: THE PATHOPHYSIOLOGICAL RESPONSES TO INDUCED SAH AND SDH, AND SUBARACHNOID ARTIFICIAL CSF IN THE SPONTANEOUSLY BREATHING PRIMATE.

Three substudies comprise this investigation. (i) induced SAH, (ii) induced SDH and (iii) subarachnoid artificial CSF injection. With this type of experimental design we are documenting the different pathophysiological responses subsequent to 3 different types of intracranial insult. We wish to identify those pathophysiological responses which are: due to ICP changes alone; due to the presence of blood in different intracranial spaces; due to the presence of blood (as compared to artificial CSF) in the subarachnoid space; due to the various combinations of ICP changes, methods of changing the ICP and the type of fluid medium introduced into the intracranial subarachnoid space. With this grouping of the 3 intracranial insults and their associated pathophysiological responses we will document the mechanisms responsible for the morbidity and mortality of SAH. With this information a second major investigation (Study B) was undertaken to examine the effectiveness of treatment of one of these mechanisms in improving the outcome of SAH.

(i) The Pathophysiological Responses To Induced SAH Using Varying Volumes of Autogenous Blood In The Spontaneously Breathing Primate.

OBJECTIVES

(a) The development of an experimental technique for the investigation of induced SAH in a spontaneously breathing monkey.

(b) To examine the rCBF, vessel caliber, respiratory pattern, pulmonary and other pathophysiological responses to induced SAH.

(c) To document the pathophysiological responses with increasing SAH volume and the degree to which these responses vary with volume.

(d) To elucidate the mechanisms for morbidity and mortality in SAH in order to gain some insight into the reasons why some patients do well and others poorly following aneurysmal rupture.

(e) To document the relationship between lethal mechanisms and hemorrhage volume.

(f) To determine a so called "LD50 SAH volume" for the present experimental model, i.e. the volume that is lethal to 50% of our animals.

(g) To examine correlation between rCBF, the pathophysiological responses to the SAH, the volume used, the neurological grade and survival.

(h) To examine correlation between respiratory pattern changes, pulmonary function change, the pathophysiological responses to SAH, the neurological grade and survival.

EXPERIMENTAL DESIGN

For this particular investigation 20 monkeys were used. These animals were randomly assigned to 4 groups, each receiving a different subarachnoid hemorrhage volume.

Four experimental SAH volumes were studied, viz. 1.0, 1.33, 1.67 and 2.0 ml/kg of body weight. In the cynomolgus monkey a direct relationship exists between body weight and fresh brain weight. With respect to brain weights the SAH volumes were 0.05, 0.07, 0.08 and 0.11 ml/gm of brain weight.

In each experimental study 4 cerebral blood flow determinations, at 15 minute intervals, were made prior to the SAH. Following the hemorrhage a flow measurement was made within 10 minutes of this insult; a second post-SAH flow measurement was made 15 minutes later. Additional rCBF measurements were then carried out at 30 minute intervals during a 2 to 4 hour period.

Cerebral angiography was performed prior to the first rCBF measurement, after the fourth flow, post-SAH after flow 6, and at the end of the experimental period. At this time anesthesia was discontinued and oxygen administered for approximately 10 minutes after which the animal was allowed to breathe room air. During the recovery period the animal was carefully observed; neurological examination and grading were performed at 5 hours post-SAH. Surviving animals were graded at 20 hours post-SAH and subsequently sacrificed using Euthanyl (MTC Pharmaceuticals) or glutaraldehyde perfusion. At postmortem the brains were removed and examined as noted previously. Six of the 20 animals were sacrificed via perfusion with glutaraldehyde for electron microscopy studies of the cerebral vessels. The protocols followed for pathological examination of the brains and cerebral vessels have been outlined in the previous section.

Animals with significant subdural or intracerebral hemorrhage were excluded from the series; a total of 8 animals were in this category.

(ii) The Pathophysiological Responses to Induced SDH Using Varying Volumes of Autogenous Blood In The Spontaneously Breathing Primate.

OBJECTIVES

(a) To examine the rCBF, vessel caliber, respiratory pattern, pulmonary and other pathophysiological responses to induced SDH.

(b) To document the physiological responses with increasing SDH volume and the degree to which these responses vary with volume.

(c) To examine correlation between rCBF, the pathophysiological responses to the SDH, the volume used, the neurological grade and survival.

(d) To examine correlation between respiratory pattern changes, pulmonary function changes, the pathophysiological responses to SDH, the volume used, the neurological grade and survival.

(e) To compare and contrast the rCBF changes, the respiratory pattern and pulmonary function changes, the pathophysiological responses to the insult, neurological grade and survival subsequent to the intracranial insults of SAH, SDH and artificial CSF injection of the same volume 1.67 ml/kg of body weight.

EXPERIMENTAL DESIGN

A total of 5 monkeys was used in this study and these were randomly assigned to 3 groups, 1 group containing 1 animal, and the 2 remaining groups, 2 animals each. The "1 animal" group received 1.33 ml/kg and the remaining 2 groups received 1.67 and 2.0 ml/kq of body weight of subdural blood respectively.

The experimental protocol followed for this group was exactly the same as that of the previous substudy of SAH, including the rCBF measurements, cerebral angiography, neurological examination and postmortem study. However in this particular study the blood was injected into the pre-chiasmatic subdural space as opposed to the subarachnouid space.

The animal in the 1.33 ml/kg group died during the experiment due to technical difficulties. In the 1.67 ml/kg group 1 animal was perfused with glutaraldehyde and the other sacrificed by Euthanyl. In the 2.0 ml/kg group 1 animal died before the 20 hour point, the other was sacrificed with Euthanyl.

(iii) The Pathophysiological Responses To Subarachnoid Injection of Artificial CSF In The Spontaneously Breathing Primate.

OBJECTIVES

(a) To examine the rCBF, vessel caliber, respiratory pattern, pulmonary and other pathophysiological responses to the subarachnoid injection of artificial CSF.

(b) To use this group as a control for comparing the changes in rCBF, respiratory pattern and pulmonary function, pathophysiological responses, neurological grade, and survival subsequent to the hemorrhage of both the SAH and SDH studies.

EXPERIMENTAL DESIGN

A total of 5 monkeys was used in this study. All animals received a subarachnoid injection of artificial CSF. The experimental protocol followed for this group was the same as that of the previously described SAH substudy, except for the introduction of subarachnoid artifical CSF instead of autogenous blood.

Of the 5 experimental animals, 4 were perfused with glutaraldehyde after the 20 hour observation period. As described previously the brain and cerebral vessels were removed for separate in vitro studies: the lungs were also examined and then removed for electron and light microscopic examination.

The fifth animal in this group died before the end of the 20 hour observation period. The brain and lungs of this animal were removed, examined and weighed and prepared for photographic, pathological and histological studies.

B. STUDY B : TO STUDY THE EFFECTIVENESS OF TREATING INDUCED SAH AND SDH WITH SIMULTANEOUS INTRAVENOUS INFUSIONS OF SODIUM NITROPRUSSIDE AND PHENYLEPHRINE IN THE SPONTANEOUSLY BREATHING PRIMATE

This study consists of 3 substudies (i)/(ii)/(iii). Allen (169) has shown the simultaneous intravenous administration of sodium nitroprusside and phenylephrine to be effective in improving postoperative clinical deterioration and vasospasm in patients with SAH due to aneurysmal rupture. We investigate the effectiveness of this form of treatment in improving CBF, alleviating cerebral vasospasm, and improving the final outcome in the spontaneously breathing primate with induced (i) SAH and (ii) SDH.

This section considers the objectives and experimental design of the study of treatment of induced SAH and induced SDH using sodium nitroprusside and phenylephrine. The final substudy of this section, (iii), deals with the objectives and design of the studies involving the application of this treatment method to spontaneously breathing primates that do not receive any form of intracranial insult. The experimental design for each of the 3 substudies of this major investigation are basically the same, and will be fully outlined in the section dealing with the first substudy. Any variation in design will be discussed in the section of the substudy to which the variation pertains.

(i) Treatment Of Induced SAH With Simultaneous Intravenous Infusions Of Sodium Nitroprusside And Phenylephrine In The Spontaneously Breathing Primate.

OBJECTIVES

(a) To determine the effects of treatment with simultaneous intravenous infusions of sodium nitroprusside and phenylephrine on post-SAH rCBF, vessel caliber and other physiological parameters in the spontaneously breathing primate.

(b) To study the rCBF, vessel caliber and other pathophysiological responses post-SAH with treatment as compared to those responses without the treatment regime (Study A(i)).

(c) To determine the effectiveness of sodium nitroprusside and phenylephrine of improving post-SAH rCBF and cerebral vessel caliber.

To determine the effectivess of this treatment regime in improving post-SAH morbidity and mortality.

(d) To correlate any changes in rCBF and vessel caliber with morbidity and mortality.

(e) To determine the effectiveness of this treatment regime in treating the effects of induced SAH.

(f) To document any changes in rCBF, vessel caliber and other physiological parameters following cessation of sodium nitroprusside and phenylephrine treatment.

EXPERIMENTAL DESIGN

A total of 8 monkeys was utilized in this study. There were 4 cerebral blood flow determinations performed at 15 minute intervals prior to the SAH as was the case with STUDY A. All animals received an SAH of 1.67 ml/kg weight of fresh autogenous blood; the so called "LD50" volume determined from STUDY A. This volume was used throughout this treatment series. In this way all the parameters of the treated series and the untreated series of the same hemorrhage volume could be compared. Following the hemorrhage, a fifth flow measurement was made within 10 minutes of the insult. At the completion of this flow 2 intravenous units were set-up into peripheral leg or arm veins. Sodium nitroprusside in a concentration of 100 ugm/ml of 5% D/W was started first, the rate being slowly increased until there was a drop in MaBP of at least 10-20 mm Hg. There was also an increase in HR of approximately 20 beats/minute. Phenylephrine, in a concentration of 8 ugm/ml in 5% D/W, was then administered through the other intravenous line. These drugs were administered simultaneously and controlled using IVAC systems (IVAC(R) Corporation) by which means we attempted to maintain the MaBP at pre-SAH levels. The dosages of the drugs were consistently varied and balanced in order to maintain a stable MaBP. The dosages used ranged from 1.31-4.30 ugm/kg/min. for sodium nitroprusside with a mean total dose of 449.64±80.76 ugm/kg over a mean total time of 146±12 minutes, and 0.48-1.15 ugm/kg/min. for phenylephrine with a mean total dose of 107.24±13.17 ugm/kg over the same time period. We exercised care not to exceed the recommended maximum dose of phenylephrine because of the possibility of renal ischemia and renal shutdown. A mean time of approximately 25 minutes was needed to set up the intravenous and IVAC systems to institute the treatment combination and to attain a stable MaBP during treatment.

The sixth flow was carried out when the MaBP was stable, approximately 50 minutes post-SAH. The remaining 4 cerebral blood flow determinations were performed at 30 minutes intervals as was the case in STUDY A.

The sodium nitroprusside and phenylephrine therapies were discontinued following cerebral angiography on completion of the tenth flow. Ten to 15 minutes later an eleventh CBF measurement was made and it was followed by a final set of cerebral angiograms.

Cerebral angiography was performed prior to the first rCBF, after flow 4 (just prior to the SAH), post-SAH after flow 6 (treatment instituted between flows 5 and 6), after the tenth flow and after the eleventh flow when the treatment had been discontinued. The protocol for rCBF determinations and cerebral angiography is the same as for STUDY A except that 1 more rCBF and 1 more set of cerebral angiograms were performed on cessation of the therapeutic regime.

On completion of the final cerebral angiogram, anesthesia was discontinued and oxygen administered for approximately 10 minutes after which the animal was allowed to breathe room air. During this period the animal was carefully observed; neurological examination and grading were carried out at 5 hours post-SAH. None of the animals of this substudy survived the 20 hour observation period.

One animal was sacrificed by glutaraldehyde perfusion when it became apparent that there was not going to be a recovery from its state of failing vital signs (grade 5). The remaining 7 animals died spontaneously.

At postmortem examination the brains were removed in total, examined, weighed and photographed. They were stored in 10% formaldehyde and subsequently, after at least 2 weeks, re-weighed and cut into thick slices for gross pathological examination and were photographed. The brain of the animal perfused with glutaraldehyde was treated in the same fashion except that it was not weighed.

The lungs and tracheobronchial trees were removed as 1 unit, examined, weighed and infused with 10% formaldehyde. The tracheobronchial tree was then tied to prevent formaldehyde leaking out and the whole pulmonary structure was immersed in formaldehyde. After at least 2-3 weeks the lungs were sectioned, stained and underwent histological examination with the light microscope. The lungs of the glutaraldehyde perfused animal were not weighed or infused with formaldehyde but were stored in formaldehyde for 2 weeks and were then sectioned, stained and reviewed histologically as were the other lungs.

The cerebral vessels of the animal perfused with glutaraldehyde were removed and examined with the electron microscope.

Animals with significant subdural or intracerebral hemorrhage were excluded from the series; a total of 8 animals were in this category.

(ii) Treatment Of Induced SDH With Simultaneous Infusions Of Sodium Nitroprusside And Phenylephrine In The Spontaneously Breathing Primate.

OBJECTIVES

(a) To determine the effects of treatment with simultaneous intraveous infusions of sodium nitroprusside and phenylephrine on post-SDH rCBF, vessel caliber and other physiological parameters in the spontaneously breathing monkey.

(b) To study the rCBF, vessel caliber and other pathophysiological responses post-SDH with sodium nitroprusside and phenylephrine as compared with those responses without the treatment regime (STUDY A(ii)).

(c) To document and correlate changes in rCBF, vessel caliber, neurological grade and survival.

(d) To document any changes in rCBF, vessel caliber and the other physiological parameters following cessation of the sodium nitroprusside and phenylephrine treatment.

EXPERIMENTAL DESIGN

A total of 6 monkeys was utilized in this particular investigation. All animals in this series received an SDH volume of 1.67 ml/kg of body weight of fresh autogenous blood. The experimental protocol and design is the same as that described in STUDY B(i) except that the blood was injected into the subdural space as opposed to the prechiasmatic cistern. The dosages of sodium nitroprusside used ranged from 0.93-3.14 ugm/kg/min., with a mean total dose of 329.55±41.75 ugm/kg over a mean total time of 146±4 minutes, and for phenylephrine 0.38-1.60 ugm/kg/min. with a mean total dose of 118.22±32.08 ugm/kg over the same time period. Approximately 30 minutes was required to set up the intravenous and IVAC systems, to institute the treatment regime and attain a stable MaBP.

The sixth flow was performed approximately 62 minutes post-SDH. The remainder of the study followed the design described in the previous substudy (STUDY B(i)).

The animals were examined neurologically and graded at 5 hours and also at 20 hours post-SDH. The 6 animals in this study were sacrificed via Euthanyl. The brains and lungs were removed and processed as described.

(iii) The Effect Of Simultaneous Intravenous Infusions Of Sodium Nitroprusside And Phenylephrine On rCBF And Other Physiological Parameters In The Spontaneously Breathing Primate.

OBJECTIVES

(a) To determine, in the spontaneously breathing monkey, the effects on rCBF, vessel caliber and other physiological parameters of simultaneous intravenous administration of sodium nitroprusside and phenylephrine.

(b) To compare and contrast the responses of rCBF, vessel caliber and other physiological parameters to intravenous sodium nitroprusside and phenylephrine with the responses of these parameters post-SAH and post-SDH with this treatment.

(c) To determine the effects on rCBF, vessel caliber and other physiological parameters of discontinuing the sodium nitroprusside and phenylephrine after an infusion period of approximately 160 minutes.

EXPERIMENTAL DESIGN

Three monkeys were used for this substudy. As in the experimental protocol of this major study group, 4 CBF determinations were initially performed. There was no hemorrhage induction in these 3 animals and no preparation for the insult was performed, i.e. no twist drill hole or induction needle placement. Other than these differences this substudy followed the same pattern as the other treatment groups. An appropriate amount of time was allowed before the fifth rCBF determination was made, as if a hemorrhage induction was performed (delay of approximately 10 minutes).

As in the other substudies of this particular major investigation a total of about 30 minutes was required to set up the intravenous and IVAC systems, to institute treatment and to attain a stable MaBP. The drug dosages for sodium nitroprusside ranged from 1.02-3.33 ugm/kg/min. with a mean total dose of 364.23±115.10 ugm/kg over a mean total time of 151±6 minutes, and for phenylephrine 0.59-1.51 ugm/kg/min with a mean total dose of 158.05±43.29 ugm/kg over the same time period, and were consistently varied and balanced to maintain an adequate and stable MaBP as in the other groups.

The remaining 4 CBF determinations were performed at 30 minute intervals. The therapeutic regime was discontinued following the cerebral angiography after the tenth flow. The eleventh CBF determination was made approximately 10-15 minutes after cessation of the therapy, and this was followed by a final set of cerebral angiograms. The remainder of the experiment followed the protocol previously described.

The animals were neurologically examined and graded at

5 hours post-"hypothetical" insult.

Two animals died spontaneously prior to the 20 hour observation time. One animal was sacrificed with glutaraldehyde infusion when it became evident at 10 hours post-"hypothetical insult", that it's vital functions were failing. The brain and lungs of these 3 animals were processed and examined via the method previously described in these studies.

It is to be noted that because of the time required to institute the treatment regime in STUDY B, flow 6 is delayed in time when compared to flow 6 of STUDY A. In fact, flow 6 of STUDY B corresponds in time to flow 7 of STUDY A. Thus comparisons of the parameters studied in the flows of the 2 major groups will be made taking into account this difference in time, i.e. the parameters of flow 6 in STUDY B will be compared to those of flow 7 in STUDY A, and flow 7 of STUDY B to those of flow 8 of STUDY A and so on.

In the following chapter, Chapter III, the results of the 2 major investigations are presented. In the first part, the pathophysiological responses to the various intracranial insults for the 7 groups (4 SAH volume groups, 2 SDH volume groups and the artificial CSF group) are presented and compared. In the second part, the responses to the insults (SAH,SDH), as well as to the treatment regime (sodium nitroprusside and phenylephrine) are compared for the SAHRx, SDHRx and Rx alone groups. In addition, the effectiveness of this treatment program was assessed by comparing the post-insult cerebrovascular responses, as well as the neurological status of the treated and untreated SAH groups (SAHRx vs 1.67 ml/kg SAH).

Comparisons are on the basis of trends and statistical analysis. The statistical tests used are the paired and unpaired "t" tests. Significances are described as no significant difference (ns), 5% probability ($p<0.05$) and 1% probability ($p<0.01$).

The measured parameters are expressed in this thesis as a mean (x) and standard error of the mean (SEM=±). All post-insult parameter values for each group are compared to their respective pre-insult mean (mean of the 4 pre-insult values). The post-insult measurements, at corresponding CBF determinations, are compared across the various groups as described. Similarly, the degree of change post-insult from the pre-insult mean for these parameters is also compared across the groups.

Concerning the recorded measurements, in order to prevent the introduction of error due to mechanical fluctuations and/or environmental effects, changes in MaBP and CPP were considered real if they were greater than 8 mmHg, and for ICP if they were more 4 mmHg.

In the text, the cerebral blood flow designation is expressed as CBF( ).

CHAPTER III

RESULTS

I. STUDY A: THE PATHOPHYSIOLOGICAL RESPONSES TO INDUCED SAH, SDH, AND SUBARACHNOID ARTIFICIAL CSF INJECTION IN THE SPONTANEOUSLY BREATHING PRIMATE.

(i) The Pathophysiological Responses To Induced SAH Using Varying Volumes Of Fresh Autogenous Blood In The Spontaneously Breathing Primate.

(a) Cardiovascular and Intracranial Pressure Responses

The mean weights of the monkeys in each group are shown in table 1; there are no significant differences between these weights.

Means, and standard errors of these means (SEM), for MaBP, HR, ICP and CPP recorded during each of the pre-SAH rCBF determinations for each volume group are presented in table 2. With each group there was no significant difference in MaBP or HR during the 4 flows. The ICP was first measured at the fourth flow. The CPP, a measure of the pressure head of blood flowing to the cerebral tissues, was not significantly different during the 4 flows of each group, except in group B (1.33 ml/kg) where CPP at CBF (4) was greater than that of the CBF (3) ($p<0.05$).

Typical cardiovascular, ICP and respiratory responses to an induced SAH are shown in figure 13. The first experimental parameter to respond was the ICP, then the MaBP followed by respiratory pattern changes, and finally EKG changes. The hemorrhage tended to result in increases in MaBP and ICP, bradycardia and other arrythmias, and respiratory pattern abnormalities.

The mean time for the MaBP to respond to the insult for the 4 SAH volume groups was 11 ± 1 seconds, the peak MaBP response occurred within 55 ± 5 seconds of the initiation of the hemorrhage, and the MaBP returned to normal, resting level at 296 ± 4 seconds after the initial MaBP change. The times, in the 4 experimental groups, for "MaBP to change", "MaBP to peak" and "MaBP to recover to normal" are presented in tables 3 and 4. No statistically significant differences in these times were found between the 4 groups except that MaBP "time to peak" for group D (2.0 ml/kg) was significantly longer than that of group B (1.33 ml/kg) ($p<0.05$). Also, the larger volume groups tended to take longer to peak and to recover than the other groups.

In 8 of the 20 animals in this substudy the initial MaBP response was hypotension; 3 of these animals were in the 1.0 ml/kg group, 2 in the 1.33 ml/kg group, 2 in the 1.67 ml/kg group, and 1 in the 2.0 ml/kg group. The decreases were 27 ± 9, 19 ± 9, 19 ± 1 and 10 mm Hg respectively. All of these animals eventually responded with hypertension. The mean duration of hypotension was 12 ± 2 seconds and was similar for all 4 groups.

In the remaining 12 animals the initial response was hypertension. The maximum, or peak MaBP responses for the groups are given in table 3, and no significant differences between these peak pressures was seen.

The general response of HR following hemorrhage, for all groups, was bradycardia within 38±9 seconds of the insult. Some difficulty was encountered in EKG interpretation since HR in these primates was rapid and the paper speed on the available recorder was not fast enough to provide a clear, accurate recording. Further, we used limb leads in this study and during the hemorrhage some of the animals assumed an opisthotonic posture with limb extension causing marked artifacts in the EKG record. These particular experimental problems were corrected (using a fast recorder and by using chest leads) in the second major investigation and in the artificial CSF group of this study. Bearing in mind the limitation described for these EKG measurements the interpretations were: all animals in the 1.0 ml/kg group demonstrated bradycardia and 1 had ventricular premature beats (VPB); in the 1.33 ml/kg group all animals experienced bradycardia, 2 had VPB's and 1 of these had a run of ventricular tachycardia; in the 1.67 ml/kg study 3 animals had bradycardia, 1 had VPB's, and another demonstrated ventricular tachycardia followed by second degree A-V block; 3 of the animals in the 2.0 ml/kg group had bradycardia, 2 of these showed ventricular tachycardia and the third ventricular bigeminy and ventricular tachycardia.

The initial response to the SAH was bradycardia, followed by the occurrence of other arrythmias (where noted). By the time of first CBF determination, post-insult, (approximately 10 minutes) the EKG for all animals had returned to normal. The HR of the 4 groups at peak ICP and at peak MaBP are presented in table 4. No significant difference were found for HR between the 4 groups at either of these 2 experimental times. The greatest decrease noted in HR and time of occurrence subsequent to the insult for each of the 4 groups were not significantly different from each other. The mean decrease was to 91±5 beats/min. at 72±11 seconds following the initiation of the hemorrhage.

In the 4 groups the average time for the ICP to change by at least 4 mm Hg was 1.7 ± 0.2 seconds. These individual times for each group are shown in table 3; no significant difference between them was noted. The mean "time to peak" for the groups was 29 ± 2 seconds, ~~and the~~ individual times for each group are presented in table 3. These times are significantly greater for the larger volume groups than for the 1.0 ml/kg group ($p<0.05$, $p<0.01$ for the 1.67 and 2.0 ml/kg groups respectively); they are also longer relative to the 1.33 ml/kg group, but significantly different only for the 2.0 ml/kg group ($p<0.05$).

The mean peak ICP for the 4 groups was 127 ± 9 mm Hg. Table 3 documents the individual peak ICP levels for the several groups. Peak ICP values for the larger volume groups were significantly greater than that of the 1.0 ml/kg group ($p<0.05$). There was no significant difference between peak ICP values for the 2 lower volume groups, nor between the values for the higher volume groups and that of the 1.33 ml/kg group.

Peak ICP occurred at the completion of the manual injection. After reaching a peak level the ICP fell quickly at first and then more gradually reaching pre-insult levels at the time of the first, post-SAH CBF determination. The only exceptions to this ICP pattern occurred in 2 animals, 1 in each of the larger volume groups, in which the ICP remained elevated (at 28 mm Hg for the animal in the 1.67 ml/kg group and at 36 mm Hg for the animal in the 2.0 ml/kg group) at the first post-SAH flow measurement. The half-time for ICP decay, as described by Steiner et al (216), is the time required for the ICP to fall to a level one-half the difference between the peak value and the initial resting value. These half-times are documented for all the groups in table 4; no significant differences were seen between groups, however, the times for the lower volume groups tended to be longer than those of the higher volume groups.

The times necessary for the ICP to return to a steady post-SAH level, i.e. a new resting state, are shown in table 4. These times are not different from one another but these values for the 1.33, 1.67 and 2.0 ml/kg groups tend to be larger than that of the 1.0 ml/kg group.

During the hemorrhage the ICP was maintained at a level less than the MaBP. Since a clinically spontaneous subarachnoid hemorrhage ceases at the point where the ICP approaches a level between diastolic and systolic blood pressure (110), in our investigations the hemorrhage was performed manually and consequently we were able to control the ICP elevation and maintain it at a level some 10-20 mm Hg below MaBP, thereby remaining within a physiological acceptable situation.

Mean cerebral perfusion pressure ($\overline{CPP}$), (calculated as MaBP-ICP, during the time the ICP responds to the insult until peak ICP) is an indication of the cerebral perfusion pressure during the insult. These values are presented in table 4 and no significant differences are evident between them. Mean cerebral perfusion pressure calculated during the time from peak ICP until the ICP returned to a steady state level ($\overline{CPP1}$) (either to pre-insult normal limits or a new resting level as discussed for "time for ICP to recover") are shown in table 4; they are not different from one another. The reason for $\overline{CPP1}$ values lying between "normal" and "high" levels post-insult, during the period that both the MaBP and ICP are falling, is that the ICP falls more rapidly than MaBP, and thus, despite an elevated ICP, $\overline{CPP1}$ remains normal or elevated during this period.

After the insult the various physiological parameters returned to new steady state levels; the values are shown in table 5. During CBF (5) MaBP for the 4 groups tended to be lower than their respective pre-SAH values. The differences were significant only for the 1.33 and 2.0 ml/kg groups ($p<0.05$). The decreases seen in the higher volume groups tended to be greater than those for the other 2 groups.

By the second post-SAH flow MaBP values for the smaller volume SAH groups had returned to normal and remained at this level during the ensuing 5 CBF determinations. With respect to the larger volume groups, MaBP tended to remain lower than resting level during the 6 post-SAH CBF evaluations. Significant decreases were seen for the 2.0 ml/kg group at CBF (6) ($p<0.01$); at CBF (7) the MaBP was within normal limits, but it remained lower than normal for the duration of this particular study.

The EKG and HR for all 4 groups had returned to normal by the fifth CBF determination, and remained this way throughout the studies.

In general, the ICP in all 4 groups returned to resting levels at the time of the fifth CBF determination. In the 1.0 ml/kg group 4 animals had normal ICP at CBF (5), but in 1 animal the ICP remained elevated at approximately 20 mm Hg until CBF (7) at which time it had returned to normal. In the 1.33 ml/kg group 2 animals had normal ICP at CBF (5), but then experienced an ICP increase during CBF (6) which persisted throughout the study at levels of 20 and 30 mm Hg respectively. The remaining 3 animals in this group had normal ICP values at CBF (5) for the remainder of the study. All animals in the 1.67 ml/kg group had normal ICP at CBF (5); 1 of these demonstrated an ICP increase at CBF (6) (to 30 mm Hg) that persisted.

In the 2.0 ml/kg group 3 animals had normal ICP values at CBF (5), 4 by CBF (7), and the remaining animal had a persistently elevated ICP (at 45 mm Hg) and died during CBF (8). The remaining 4 animals maintained normal ICP values for the duration of the studies.

The CPP of the 4 SAH volume groups followed the combined changes of both ICP and MABP. In the 1.0 ml/kg group the CPP returned to pre-SAH resting levels by CBF (5) and remained normal throughout the duration of the experiments. During CBF (5) the CPP values of the other 3 groups remained significantly lower than their respective resting status ($p<0.05$) (figs. 14-17; tables 5 and 6). This situation results from low MaBP, since the ICP in general had returned to normal by CBF (5). After this flow, the CPP of the 1.33 ml/kg group returned to normal for the duration of the studies. It should be noted that the largest decreases in CPP are experienced by the higher SAH volume groups.

For these larger volume groups there was some recovery of the CPP, but as was the case with MaBP, CPP tended to remain lower than normal and below that of the lower volume groups throughout the remaining CBF determinations. This decrease was significant for the 2.0 ml/kg group at CBF (6) ($p<0.05$). At CBF (7) the CPP of this group approached the normal value, but fell again by CBF (8) and remained lower than resting. The persistent CPP reduction resulted from the tendency for the MaBP values of these 2 groups to remain low.

(b) Respiratory Pattern and Arterial Blood Gas Changes.

The respiratory parameters monitored were tidal volume (Vt) and respiratory rate (RR). Mean values of Vt and RR for each of the pre-SAH flows for each group are presented in table 7. No significant differences were found between the Vt values in the 4 pre-insult flows of each group except for the 1.0 ml/kg group, where the Vt of the first flow was greater than that of CBF (4) ($p<0.05$), and in the 1.67 ml/kg group where the Vt of CBF (4) was greater than that of CBF (3) ($p<0.05$). However these differences are quite small, in the order of 2 ml. Overall mean Vt values during the 4 flows for each group are also given in the table 4.

No statistically significant differences were found between the 4 pre-insult RR values within each group. The overall means for these rates are shown in table 4.

Arterial blood gases, pH and A-aDO2 measured during the pre-SAH period for the groups are presented in table 7. There was no significant difference between the 4 pre-SAH values for PaCO2, PaO2, pH and A-aDO2 in each group. The overall mean values are also shown.

The initial changes in Vt and in RR, subsequent to the SAH, were variable; increases, decreases and no changes were demonstrated. The average times for the respiratory pattern to change for each group are shown in table 3, and there is no significant difference between them. In most animals the initial respiratory responses progressed to further changes, consisting of varying periods of apnea that began during the hemorrhage and persisted after its completion (fig. 13). Subsequent to the apnea, recovery of respiration occurred in all animals. Apnea occurred with 3 animals in the 1.0 ml/kg group, 4 in the 1.33 ml/kg group, and 5 in both the 1.67 and 2.0 ml/kg groups. The durations of apnea for these groups are shown in table 3. The larger volume groups experienced longer periods of apnea than did the lower volume groups. Both the 1.67 and 2.0 ml/kg groups had periods of apnea significantly greater than that of the 1.0 ml/kg group, ($p<0.01$, $p<0.05$ respectively). These larger volume groups also had longer periods of apnea than did the 1.33 ml/kg group but it was significant only for the 1.67 ml/kg group ($p<0.01$). There was no significant difference in these time periods between the 2 lower SAH volume groups, or between the 2 larger SAH volume groups.

The 3 animals not experiencing apnea developed bradypnea and nonspecific respiratory rhythm irregularities during the hemorrhage; one of these also demonstrated a large increase in Vt.

The "time for respiration to recover" is defined as the time from the initial respiratory change subsequent to the insult up until the recovery of regular respiratory rhythm. This point was chosen since we believe it to indicate a return to normal in respiratory centre function (regular rhythmic respirations). Another factor influencing this choice was the development of increased Vt in the larger volume groups on the resumption of respirations following the apneic episode. The respective "time to recover" for the groups are shown in table 4. The larger volume SAH groups took longer to recover than did the smaller volume groups. This recovery time was statistically significant only for the 1.67 ml/kg group relative to the 1.0 ml/kg group ($p<0.01$). No differences between these times were found for the 1.0 and 1.33 ml/kg groups, or between those of the 1.67 and 2.0 ml/kg groups.

With respect to the respiratory pattern changes resulting from SAH the higher volume groups experienced apneic episodes more frequently, and of longer duration, as well as longer periods of time to recover regular respirations than did the lower volume groups.

Arterial blood gases and pH measurements were not made during the hemorrhage induction.

Tables 8 and 9 give the post-SAH values of Vt, RR, PaCO2, PaO2, A-aDO2 and pH. The respiratory pattern parameters and the arterial blood gases are expressed as percentages of the appropriate pre-insult values, and the A-aDO2 and pH values are expressed in absolute units. PaO2, PaCO2 and A-aDO2 ,pre and post-SAH, are shown in figures 18 and 19.

During CBF (5) Vt in the 1.0 ml/kg group was slightly less (ns) than the resting level, that of the 1.33 ml/kg group was normal, and the values for the 1.67 ml/kg and 2.0 ml/kg groups (148±24% and 142±24%) were greater (ns) than the respective resting levels. Respiratory rate in all groups returned to normal by CBF (5) (11±2 minutes post-SAH).

PaCO2 in the lower volume groups was always within normal limits by CBF (5); PaCO2 in the larger volume groups was lower than normal (ns). The largest PaCO2 decrease at this flow was experienced by the 1.67 ml/kg group (76±9% of normal). Similarly PaO2 values of the lower volume groups were normal, and those of the larger groups were lower than resting (ns). PaO2 in the 1.67 ml/kg group was lowest at 83±13% of normal.

A-aDO2 in the 1.0 ml/kg group increased slightly above normal, whereas significant increases ($p<0.05$) were experienced by the higher volume groups. The 1.33 ml/kg group did not develop any changes in A-aDO2.

pH in the 1.0 ml/kg groups was unchanged, that of the 1.33 ml/kg group decreased slightly (ns), and those of the higher volume groups increased (ns).

The respiratory patterns in all 4 groups returned to within normal limits by CBF (6) (28±2 minutes post-SAH). There were fluctuations in both Vt and RR values (ns), especially in the higher volume groups, for the duration of the studies.

PaCO2 in the lower volume groups remained normal for the subsequent 5 CBF determinations (fig. 19(b)). In the larger SAH volume groups PaCO2 remained lower than normal (ns) at CBF (6) but returned to normal at CBF (7) and for the duration of the studies (fig. 19(b)).

PaO2 for the 1.0 and 1.33 ml/kg groups were normal throughout the experiment. For the higher volume groups, PaO2 remained lower than normal (ns) up until CBF (9) for the 1.67 ml/kg group and CBF (8) for the 2.0 ml/kg group (fig. 19(a)).

A-aDO2 for the 1.0 ml/kg group remained slightly elevated (ns) at CBF (6,7,9,10) and was normal at CBF (8). In the 1.33 ml/kg group A-aDO2 remained slightly below normal for the duration of the studies. This was significant at CBF (7,8,9) ($p<0.05$) (fig. 18(a); tables 8 and 9).

A-aDO2 in the 1.67 ml/kg group remained elevated (ns) but gradually decreased during the ensuing CBF determinations. A-aDO2 of the 2.0 ml/kg group remained elevated (ns) up to and including CBF (7), after which it fell abruptly to normal levels (fig. 18(a); tables 8 and 9). The A-aDO2 elevations for the 2 smaller volume groups were similar as were those of the larger volume groups. The latter were consistently greater than the A-aDO2 elevations experienced by the lower volume groups.

pH in the 1.0 ml/kg group was slightly decreased (ns) during CBF (7), and increased (ns) during CBF (9). Otherwise it remained at normal levels. For the 1.33 ml/kg group pH remained slightly lower than resting (ns) at CBF (7,8,9,10). For the 1.67 ml/kg group after CBF (5) pH fell slightly (ns) at CBF (7), but was normal for the other CBF determinations. pH in the 2.0 ml/kg group remained low (ns) for CBF (7) to CBF (10) inclusive.

The larger volume SAH groups experienced greater increases in Vt and A-aDO2, and larger decreases in PaCO2 and PaO2 than did the smaller volume groups.

Subsequent to the hemorrhage, 4 animals died acutely, 2 in each of the larger volume groups. In each of these animals respiratory arrest occurred followed by cardiovascular decompensation and death. In the 1.67 ml/kg group the 2 animals died prior to CBF (6). Both of these animals developed hypoxemia post-SAH (50 and 18 mm Hg). At the time of the PaO2 determinations the animals were experiencing respiratory difficulty and were deteriorating rapidly. It was therefore difficult to establish whether the decreases noted in the PaO2 levels were due to the respiratory difficulties or due to some other factors. Calculations of the A-aDO2 help to delineate the aetiology of the hypoxemia. Figure 18(b) shows that the animals dying in the 1.67 ml/kg group had greater increases in A-aDO2 than did the survivors. Also, A-aDO2 for the animals dying did not recover whereas A-aDO2 for the survivors gradually decreased towards normal. This is the mirror image of the PaO2 values in this group. Both the dying and surviving animals developed decreases in PaO2. Those animals dying developed a greater degree of hypoxemia that did not recover compared to the survivors where the low PaO2 returned to normal.

Of the 2 animals dying acutely in the 2.0 ml/kg group, 1 died after CBF (7) and the other just prior to CBF (8). The PaO2 decreases in these 2 animals were larger than those seen in the 3 surviving animals,and thus, for the most part were responsible for the PaO2 decrease seen post-SAH in this group (fig. 19(a); tables 8 and 9). This explains the rapid return to normal of PaO2 at the CBF (8). The slight decrease in PaO2 in the surviving animals had recovered to normal by CBF (7), but this fact is masked by the low PaO2 values for the other 2 animals. This situation is also illustrated in the A-aDO2 values for this group, figure 18(a). The 2 animals dying had large increases in A-aDO2 post-SAH, whereas A-aDO2 in the surviving animals remained normal. This explains the increase in A-aDO2 demonstrated in figure 18(a)(b) for this group and the rapid return to normal values at CBF (8).

Those animals in the larger volume groups had greater increases in A-aDO2 and larger decreases in PaO2 than experienced by the lower volume groups.

(c) Regional Cerebral Blood Flow and Cerebrovascular Resistance Changes.

Regional cerebral blood flow and the CVR index values for the pre-SAH CBF determinations are presented in table 2. No significant differences were present between the rCBF levels or CVR indices at the 4 pre-insult CBF determinations within each group. The overall mean values of these physiological parameters are also presented in the table.

The pre and post-SAH rCBF values for all the groups, are presented in figures 14-17 along with their respective PaCO2 and CPP levels at the time of the CBF determination. IDICA caliber is also shown. The post-SAH rCBF values, expressed as percentages of resting levels, are presented in tables 5 and 6.

The response of rCBF to the SAH insult was a reduction in flow (figs. 14-17; tables 5 and 6). The first CBF measurement following the insult, CBF (5), was within 11±2 minutes of the hemorrhage induction. Mean rCBF values at CBF

(5) for the 4 groups in order of increasing volumes were, 35±5, 39±5, 18±2 and 18±4 ml/100gm/min. These rCBF values are all less than their respective resting values. The decreases are statistically significant in the 1.0 ml/kg group ($p<0.05$), the 1.67 ml/kg group ($p<0.05$) and the 2.0 ml/kg group ($p<0.01$). The greatest decreases in rCBF were experienced by the larger volume groups.

Figure 20(a) depicts CVR values pre and post-SAH. All 4 groups show increases (ns) in CVR at CBF (5). The largest increases in CVR were experienced by the larger volume groups.

The rCBF values in all groups showed improvement by CBF (6), but remained below resting levels. This reduction was statistically significant for the 1.0 ml/kg group ($p<0.05$) and the 2.0 ml/kg group ($p<0.01$). The rCBF in the 1.0 ml/kg group continued to improve throughout the duration of the studies, but remained slightly less than resting levels. This decrease was significant only at CBF (7) ($p<0.05$).

In the 1.33 ml/kg group rCBF returned to normal at CBF (7) and remained normal during the following CBF determination.

The rCBF in the 1.67 ml/kg group remained lower than normal (ns) throughout the ensuing investigations.

In the 2.0 ml/kg group rCBF remained low throughout the experimental studies. These reductions were significant at

CBF (7) ($p<0.05$), CBF (8) ($p<0.05$) and CBF (9) ($p<0.01$). There was an improvement in rCBF in this group at CBF (8) to 85±4% of normal, but it was still significantly lower than resting.

Figure 20 and tables 5 and 6 demonstrate that the CVR index of the 1.0 ml/kg group remained slightly greater (ns) than resting values and this was significant at CBF (8) ($p<0.01$). In the 1.33 ml/kg group the CVR index returned to normal at CBF (6) and remained so for the duration. With respect to the 1.67 ml/kg group, the CVR index decreased slightly after the fifth flow, but remained elevated (ns) above resting levels for the remainder of the studies. One value, at CBF (9) was statistically greater from normal ($p<0.05$).

The CVR in the 2.0 ml/kg group remained elevated (ns) above resting, for CBF (6) and CBF (7). After CBF (7) CVR returned to normal levels and remained so for the ensuing flows.

The larger volume SAH groups experienced greater initial decreases in rCBF and larger increases in CVR than did the smaller value groups. In the 1.67 ml/kg group rCBF values remained low, and the CVR values higher, than those of the 2 smaller value groups. This was also the case with rCBF and CVR in the 2.0 ml/kg group up until CBF (8), at which point the rCBF showed some recovery, and the CVR returned to normal. However, the rCBF values of this group did remain lower than resting, but not significantly different from the comparable values in the 1.0 ml/kg group.

In the 1.67 ml/kg group, 1 animal died before and 1 after the first post-SAH CBF measurement. rCBF of the animal dying after CBF (5) was 14 ml/100gm/minute, 22% of its pre-insult resting value. This value was lower than that of the other animals in the group at this flow measurement. Figure 21(a) shows rCBF for each group for the animals surviving the complete experimental studies. Figure 21(b) shows rCBF for each of the animals dying acutely. As noted, for the 1.67 ml/kg group, 1 animal died before the CBF (5), and the other, which survived until the end of CBF (5) had a lower rCBF than did the surviving 3 animals. In the 2.0 ml/kg group, 2 animals died immediately after CBF (7). The rCBF values of these animals at CBF (5) were less than the corresponding flows for the remaining 3 animals of the group. These values were 7 and 12 ml/100gm/minute respectively, representing, 14% and 33% of their resting levels. rCBF in these 2 animals remained low until death and were definitely lower than the corresponding flow values of the other 3 animals of this group (fig. 21(a),(b)). rCBF at CBF (7), just prior to their demise, were 17 and 11 ml/100gm/minute respectively, representing 34% and 30% of their normal values. This explains the marked improvement in rCBF in the 2.0 ml/kg group during the transition from CBF (7) to CBF (8) as seen in tables 5 and 6 and figure 17. It appears that the low rCBF in these 2 acute deaths weighted the overall mean rCBF of the group during CBF (6) and CBF (7). Despite the gradual improvement in rCBF in the surviving animals during CBF (6,7,8) as shown in figure 21(a), it appears more marked in figure 17 and tables 5,6 because the 2 animals died and no longer contributed to the mean rCBF after CBF (7).

The animal dying in the 1.67 ml/kg group experienced a greater increase in CVR than did those surviving (fig. 20(b)). CVR increased to 5.14 whereas the mean value in the surviving animals at CBF (5) was 3.46.

CVR for the 2 acute deaths in the 2.0 ml/kg group were greater than those of the surviving animals (fig. 20(b)). The 3 surviving animals experienced a CVR increase at CBF (5) but it returned to normal at CBF (6) and remained so for the duration of the studies. Figure 20(a) shows the persistent elevation of CVR in the 2.0 ml/kg group post-SAH up until CBF (7) after which CVR returned to normal. The reason for this pattern, is similar to that previously explained for the rCBF changes in the group. In this case the increased CVR in the dying animals pulled the overall CVR mean upward until their demise (following CBF (7)) after which the CVR was normal.

In the larger volume groups, those animals dying acutely had greater decreases in rCBF and greater increases in CVR than those surviving.

(d) Cerebral Angiography

As previously discussed in chapter II (Methods) vessel calibre was measured only for the large intradural capacitance vessels; intradural internal carotid artery (IDICA) above and below the origin of the posterior communicating artery (C1,C2), middle cerebral artery (MCA) and the proximal pericallosal artery (CA). The data obtained from measurements of the intradural internal carotid artery (C2) will be presented in the text. This vessel was most consistently well visualized on the lateral cerebral angiograms, and thus measurements at this site provided the most complete and accurate assessment of cerebral vessel calibre during the studies. Measurements of other vessels (C1,MCA,CA) revealed, that in general, they responded in similar fashion to the insult of subarachnoid hemorrhage as did C2. Thus, we believe that IDICA, C2 measurements accurately reflect the status of the cerebral vasculature during the experimental investigations.

Cerebral angiography (lateral) studies were performed immediately following the neck surgery to demonstrate placement of the aneurysm clip occluding the external carotid artery and precise positioning of the common carotid artery catheter at the origin of the internal carotid artery (fig. 22) Baseline cerebral angiography was performed approximately 15±2 minutes prior to the subarachnoid hemorrhage induction.

The mean pre-SAH IDICA diameters for the 4 groups are shown in table 2. These measurements are considered as normal resting values. Following the insult, the first set of cerebral angiograms was perfomed immediately following CBF (6). The second and final series of angiograms was perfomed at the conclusion of the experimental studies, after CBF (10). The post-injection IDICA vessel calibres for the 4 groups are presented as a percentage of normal in tables 5,6. Actual vessel measurements at these determinations are shown graphically in figures 14-17. Representative cerebral angiograms for the 4 groups during the pre and posh-SAH periods are presented in figures 23(a),(b),(c)-26(a),(b),(c).

The initial response to the insult of the 4 groups was diffuse vasospasm. There was no observable difference in the degree of vasospasm of the groups (figs. 23(b)-26(b)).

There was a significant reduction in the size, from resting, of the IDICA in all the groups (1.0, 1.33, 1.67-$p<0.01$, 2.0-$p<0.05$). However, the degree of spasm experienced was not significantly different for the 4 volume groups.

Cerebral angiography following CBF (10) demonstrated some recovery of vessel diameter in all groups (figs. 23c-26c). This recovery appeared to be more complete for the 2 lower volume groups. The IDICA diameter increased, but remained lower than control in all 4 groups. This was significant only for the 1.67 ml/kg SAH group ($p<0.05$). As was found at the first post-SAH angiographic examination, the degree of cerebral vasospasm observed at this study was not significantly different between the 4 groups.

(ii) The Pathophysiological Responses To Induced SDH Using Varying Volumes Of Fresh Autogenous Blood In The Spontaneously Breathing Primate.

This experimental group comprises 4 animals, 2 with 1.67 ml/kg and 2 with 2.0 ml/kg hemorrhages. At post-mortem examination of the brains, it was found that despite most of the injected blood being subdural, there was always some subarachnoid blood. We found it impossible to determine the percentage or ratio of subarachnoid to subdural blood. For this reason, as well as the fact that the number of experimental animals in this group were few, we are only presenting the results of the SDH study for general interest, and are generally not comparing them to the results of the other groups. No statistical analysis was carried out on the results of this group.

It is also to be noted, that due to mechanical failure, we were unable to record the physiological parameters at the final CBF determination (CBF (10)) in 1 of the 2.0 ml/kg animals.

(a) Cardiovascular and Intracranial Pressure Responses

The mean weights of the monkeys in each group are shown in table 1. The means and SEM's for MaBP, HR, ICP, and CPP for each group recorded during each pre-insult CBF determination are shown in table 10. Typical cardiovascular, ICP and respiratory responses to an induced SDH are shown to be similar to the SAH groups, and are presented in figure 27. As was found in the SAH groups, the first parameter to change was ICP, followed by MaBP, and then the respiratory pattern changes. The EKG responses were again last to occur, consisting mainly of sinus bradycardia.

The mean times for ICP, MaBP and respiratory pattern to change are shown in the table 11, and are similar to those of the larger volume SAH groups.

In the 1.67 ml/kg group, 1 animal responded to the insult with hypertension, and the other with hypotension. The MaBP decrease was 10 mmHg, lasting for 5 seconds, and was then followed by hypertension. In the 2.0 ml/kg group, both animals responded with hypotension, which was then followed by a hypertensive response. The mean decrease was 15±1 mmHg lasting for 16±1.0 seconds. Peak MaBP values and times to peak are shown in table 11, and MaBP times to recover in table 12.

The general HR response was sinus bradycardia. The greatest decrease in HR was to 112±28 beats/minute occurring at 91±28 seconds post-insult initiation. The HR at peak ICP and MaBP for the 1.67 ml/kg group are shown in table 12. In both of the 2.0 ml/kg group animals, the EKG recorder malfunctioned at these times.

The times to peak and the peak values for ICP of the SDH groups are shown in table 11, and are similar to those of the larger SAH volume groups. The ICP "half-time decay" and "time to recover" values are presented in table 12. The "time to recover" times for the SDH groups were shorter than those for the same volume SAH groups, and the ICP "half-time decay" values were similar.

As was the case with the SAH groups, ICP was maintained 10-20 mmHg below MaBP during the injection. The $\overline{\mathrm{CPP}}$ and $\overline{\mathrm{CPP1}}$, values for the SDH groups are shown in table 12, and are seen to be similar to those of the larger volume SAH groups.

Following the insult, the various physiological parameters returned to new steady state levels. The post-SDH MaBP, ICP and HR values are shown in table 13. During CBF (5), MaBP for both SDH groups tended to be lower than their respective pre-insult levels. In the 1.67 ml/kg group, MaBP tended to recover during the ensuing investigations whereas that of the 2.0 ml/kg group remained somewhat decreased.

The ICP in both groups returned relatively quickly to resting levels and remained so, except for 1 animal in the 1.67 ml/kg group, whose ICP increased to 18 mmHg at CBF (8) and remained at this level until the end of the experiment.

The CPP values followed the combined changes in MaBP and ICP. These CPP levels tended to remain lower than pre-SDH values. This was more marked for the 2.0 ml/kg group than the 1.67 ml/kg group.

(b) Respiratory Pattern and Arterial Blood Gas Changes.

Mean pre-SDH Vt, RR, arterial blood gas pH and A-aDO2 values during each of the first 4 CBF determinations for the 2 groups are shown in table 14.

The initial changes in Vt and RR were variable, as was documented for the SAH groups. The times for the respiratory pattern to change are shown in Table 11. All 4 animals developed periods of apnea. The mean durations of apnea for the 2 groups are shown in table 11, and are seen to be shorter in duration than that experienced by similar volume SAH groups. The times to recover regular respirations are shown in table 12. These times are shorter than those of the larger volume SAH groups (faster recovery for the SDH groups).

Arterial blood gas, pH and A-aDO2 determinations were not made during the hemorrhage.

Table 15 gives the post-SDH Vt, RR, PaCO2, PaO2, pH and A-aDO2 values. The Vt, RR, PaCO2 and PaO2 values are expressed as percentages of the pre-insult values, and the pH and A-aDO2 values are expressed in absolute units. PaCO2, PaO2 and A-aDO2 absolute values both pre and post-SDH are graphically represented in figures 28(a),(b) and 29.

In general Vt for the 2 groups remained at least initially unchanged following the insult. Towards the end of the experiments, Vt tended to decrease slightly. Similarly, RR remained unchanged in the early stages following the SDH, but tended to increase towards the end of the studies.

At CBF (5), PaCO2 of both groups was lower than resting, but following this, the values were essentially no different from pre-insult levels (fig. 28(b); table 15).

Similarly, PaO2 did not change following the SDH, and remained normal for the duration of the studies (fig. 28(a); table 15).

During the 6 CBF determinations after the SDH, A-aDO2 values tended the remain slightly elevated for both groups, compared the pre-insult levels (fig. 29; table 15).

The pH values of the 1.67 ml/kg group did not change, whereas those of the 2.0 ml/kg group were, in general, elevated following the insult (table 15).

(c) Regional Cerebral Blood Flow and Cerebrovascular Resistance Changes

Regional cerebral blood flow and CVR index values for the 4 pre-SDH CBF determinations are shown in table 10. These pre and post-SDH values for the 2 groups, along with their respective IDICA diameters, CPP and PaCO2 values are shown in figures 30,31. The post-SDH values expressed as percentages of resting are presented in table 13. This table also documents the CVR values in absolute units.

The initial response of rCBF to the insult was a reduction in flow. This response was much more marked in the 2.0 ml/kg group. The rCBF remained decreased for the remainder of the studies in the 2.0 ml/kg group, but returned to normal following CBF (5) in the 1.67 ml/kg group.

The pre and post-SDH CVR values are graphically presented in figure 32. The CVR of the 1.67 ml/kg group decreased slightly at CBF (5), and was normal for the duration of the studies. For the 2.0 ml/kg group, CVR was elevated following the SDH and remained so for the duration (fig. 32; table 13).

As has been mentioned, because of the small number of animals in this SDH study, as well as the presence of both subarachnoid and subdural blood, no firm statements about these SDH group results, or hard comparisons with the SAH groups of similar volumes can be made. However, some definite differences and trends were elicitied:

(i) Times for ICP to recover were shorter for the SDH groups compared to similar volume SAH groups.

(ii) The durations of apnea and times to recover regular respiration were shorter for the SDH groups compared to the SAH volume groups of similar volume.

(iii) The degree of post-insult respiratory pattern disturbances were more marked in the SAH groups.

(iv) The changes in arterial blood gases and A-aDO2 were more marked in the larger volume SAH groups compared to the SDH groups.

(v) Following the insult, rCBF decreased and CVR increased in the 2.0 ml/kg SDH group, in similar fashion to that of the larger volume SAH groups. In the 1.67 ml/kg SDH group, these parameters both decreased slightly immediately following the hemorrhage, and then quickly recovered.

(d) Cerebral Angiography

The mean pre-insult IDICA diameters for the 2 groups are presented in table 10. Post-SDH IDICA caliber, expressed as a percentage of resting, is shown in table 13. The actual pre and post-SDH IDICA measurements are graphically shown in figures 30 and 31.

The cerebral angiograms in figures 33(a),(b),(c) and 34(a),(b),(c) are representative of pre and post-SDH states of the cerebrovasculature in the 2 SDH groups.

Both groups demonstrated cerebral vasospasm following the insult, similar in degree to that seen in the same volume SAH groups (figs. 30 and 31; tables 5 and 13).

The final angiogram and IDICA measurement showed complete recovery of spasm in the 1.67 ml/kg SDH group, whereas no recovery was seen in the 2.0 ml/kg SDH group (figs. 30 and 31; table 13). This latter response is similar to that occurring in the larger volume SAH groups (table 6).

(iii) The Pathophysiological Responses To Induced SAH With 1.67 ml/kg Of Body Weight Of Fresh Autogenous Blood And To The Subarachnoid Injection Of 1.67 ml/kg Of Body Weight Of Artificial CSF (Elliott's "B" Solution) In The Spontaneously Breathing Primate.

(a) Cardiovascular and Intracranial Pressure Responses.

The mean weight of the experimental animals in the artificial CSF group is shown in table 1; it is not significantly different from that of the 1.67 ml/kg SAH group.

The means and SEM for MaBP, HR, ICP and CPP in both groups for the 4 pre-insult CBF determinations are presented in table 2. Within the 1.67 ml/kg SAH group there were no significant differences in MaBP values, HR or CPP recorded during these 4 flows. The ICP was first measured at CBF (4). For the artificial CSF group, both MaBP and CPP at the fourth flow were significantly greater than the corresponding values at CBF (3) ($p<0.05$). The actual differences were 8 and 9 mm Hg respectively. As discussed in Chapter II, we considered true changes in MaBP and CPP to be present if there was more than an 8-10 mm Hg difference. The HR at CBF (4) was significantly greater than that at CBF (1) ($p<0.05$), but the difference was only 12 beats/minute. The mean values of these parameters over the 4 flows are also shown in table 2. No other statistically significant differences were found. The ICP, as for the 1.67 ml/kg group, was recorded during the last pre-insult flow.

Typical cardiovascular, ICP, respiratory pattern and RVP responses to the injection of artificial CSF are documented in figure 35. The first parameter to respond was the ICP followed in sequence by the MaBP, respiratory pattern, RVP and HR. The insult, as already documented for the 1.67 ml/kg SAH group, caused increases in MaBP and ICP, bradycardia and other arrythmias and respiratory pattern irregularities

The RVP was increased subsequent to the injection. After the insult the MaBP, ICP, and RVP gradually returned to normal levels as did the EKG and HR.

The mean times for the "MaBP to change", "MaBP to peak" and "MaBP to recover to normal" for the 2 groups are shown in tables 3 and 4. There were no significant differences between these times in the 2 groups, although the time for "MaBP to peak" tended to be longer for the 1.67 ml/kg SAH group.

The initial response of MaBP in the artificial CSF group in 2 animals was hypotension with a mean decrease of 17±5 mm Hg from resting levels with a duration of approximately 16±1 seconds. These particular animals recovered and progressed to a hypertensive state. The remaining 3 animals experienced hypertension as the initial response. In the 1.67 ml/kg SAH group there were also 2 animals responding initially with hypotension. The mean decrease was 19±1 mm Hg, and the duration was 14±2 seconds.

Peak MaBP responses for the 2 groups are shown in table 3. No significant difference was present between the 2 peak pressures.

The HR response in artificial CSF group subsequent to the hemorrhage was initially bradycardia, with onset 25±4 seconds after the initiation of the insult and subsequent to the changes in ICP, MaBP and respiratory pattern. This sequence of events was similar to that seen in the 1.67 ml/kg SAH group. For the artificial CSF group investigations we used a faster recording system, and chest leads instead of limb leads. With these improvements in technique we were able to interpret the EKG responses more readily. The bradycardia seen was that of sinus bradycardia. Other arrythmias seen were junctional rhythms, supraventricular premature beats, ventricular tachycardia and PVB's. Nonspecific T wave changes and ST elevations were present. The HR for both groups at peak ICP and peak MaBP are shown in table 4. The values at the respective pressure peaks were not different between the 2 groups. The HR in both groups were slower at peak MaBP than at peak ICP. The HR of the 2 groups at peak ICP tended to be greater than their respective pre-insult resting levels; the rates at peak MaBP were slightly less than resting levels.

The slowest HR for the artificial CSF group was 160±13 beats/min. occurring 41±7 seconds post-injection initiation and for the 1.67 ml/kg SAH group it was 90±6 beats/min at 54±9 seconds.

By the time of the first post-insult CBF determination (8±1 minutes after the injection), the EKG and HR, of all the animals in the artificial CSF group and the 4 surviving in the 1.67 ml/kg SAH group, had returned to normal.

The mean times for the "ICP to change" and "ICP to peak" are presented in table 3. There were no significant differences between the corresponding times for the 2 groups. The peak ICP levels of both groups are shown in table 4, and there were no significant differences between them. The maximum ICP response of the artificial CSF group tended to be greater than that of the SAH group. As was the case in the SAH groups, the ICP with the artificial CSF injection peaked at the completion of the injection.

After the peaks were reached, ICP levels fell rapidly at first and then more gradually. By the first post-insult CBF determination ICP levels of all animals in the artificial CSF group were normal. In the 1.67 ml/kg SAH group the ICP of 4 animals were within normal limits by this time but remained elevated in 1 animal.

The half-time ICP decay values for the 2 groups are presented in table 4, and are not significantly different. However the time for the 1.67 ml/kg SAH group tends to be longer than that for the artificial CSF group.

The mean times for the ICP to return to normal for the artificial CSF group and to a steady state for the 1.67 ml/kg SAH group are shown in table 4. For the 1.67 ml/kg SAH group this time was significantly longer than that of the artificial CSF group ($p<0.05$).

The mean cerebral perfusion pressures during the time of ICP change to ICP peak ($\overline{\text{CPP}}$) for the 2 groups are shown in table 4 and these are not significantly different. The mean cerebral perfusion pressures calculated during the period of time from peak ICP up until the steady state level post-SAH, ($\overline{\text{CPP1}}$), for both groups are recorded in table 4, and are not significantly different from one another.

After the artificial CSF insult, as was found for SAH volume groups, the MaBP, HR, ICP and CPP levels returned to a steady state. The values of these physiological parameters for the remaining 6 CBF determinations are shown in tables 5,6 as are those of of the 1.67 ml/kg SAH group.

During CBF (5) MaBP in the artificial CSF group was not different from resting levels; for the 1.67 ml/kg SAH group MaBP was lower than normal (ns). For the remainder of the studies, MaBP levels in the artificial CSF group were not different from resting levels whereas those of the 1.67 ml/kg SAH group were lower than normal (ns)

In both groups, the EKG and HR returned to normal, pre-insult status, by the fifth CBF determination. The HR for these 2 groups, post-injection, are presented in tables 5,6. For the artificial CSF group the HR was generally not different from resting levels except for significant increases at CBF (9) ($p<0.05$) and CBF (10)($p<0.01$). For the 1.67 ml/kg SAH group, there were no significant differences in post-SAH HR values from resting. However, heart rates at CBF (8,9,10) tended to be greater than normal. The increases seen in HR during these later flow measurements were not significantly different between the 2 groups.

The mean ICP in the artificial CSF group returned to normal by the first post-insult flow and remained at this level for the duration of the experimental studies (tables 5 and 6). For the 1.67 ml/kg SAH group, the ICP returned to resting level by CBF (5) and remained normal for the ensuing flows (tables 5 and 6). As discussed previously, 1 animal in this group experienced a persistently elevated ICP.

The post-insult CPP levels for the 2 groups are documented in tables 5,6 and in figures 16 and 37. For the artificial CSF group, the CPP values returned to normal by CBF (5) and remained so during the experimental studies. In the 1.67 ml/kg SAH group, the CPP at CBF (5) was significantly lower than the resting level ($p<0.05$). Throughout the remaining flows, the CPP levels of this group were persistently lower than normal (ns).

Subsequent to the insult, the changes in MaBP and CPP were greater in the 1.67 ml/kg group than in the artificial CSF groups.

(b) Respiratory Pattern, Arterial Blood Gas, Alveolar - Arterial Oxygen Difference and Right Ventricular Pressure Changes.

The mean Vt and RR values for both the artificial CSF group and the 1.67 ml/kg SAH groups are shown in table 7. For the artificial CSF group no significant differences were present between either the Vt values or the RR values during the pre-insult CBF determinations. In the 1.67 ml/kg group the only significant difference noted was in Vt with the value at CBF (4) significantly greater than that at CBF (3) ($p<0.05$). This difference however, was quite small, of the order of 2 ml. The overall mean values for the 2 respiratory parameters are also documented in table 7.

The arterial blood gases, pH and A-aDO2 values for each pre-insult flow are presented in table 7. The overall means are also shown. There were no significant differences in the PaO2, pH or A-aDO2 for the 4 flows in the 2 groups, except in the artificial CSF group, where A-aDO2 at CBF (1) was significantly greater than at CBF (4) ($p<0.05$).

In the artificial CSF group the only significant difference in the 4 PaCO2 levels was that at CBF (1), this being greater than that at CBF (4) ($p<0.05$). There were no significant differences between PaCO2 for the 4 pre-insult flows in the 1.67 ml/kg SAH group.

The pre-insult RVP levels for the artificial CSF group are presented in table 7 and there are no significant differences. The overall mean RVP for the 4 flows is also documented in table 7.

As was the case in SAH volume groups the changes of Vt and RR in the artificial CSF group subsequent to the insult were quite variable. Again, no specific pattern of respiratory changes were demonstrated (fig. 35). In both groups, these respiratory changes progressed to varying periods of apnea (figs. 13 and 35).

The mean times required for the respiratory pattern to change on initiation of the insult are shown in table 3. There is no significant difference between these times. The mean durations of apnea for both groups are also shown in table 3. The period of apnea for the 1.67 ml/kg SAH group (95±6 seconds) was significantly longer than that of the artificial CSF group (25±3; $p<0.01$). The apnea in all animals began during the injection and persisted after its cessation.

The mean times for "respiration to recover" to regular rhythm are presented in table 4, this length of time for the 1.67 ml/kg SAH group was significantly greater than of the artificial CSF group ($p<0.01$).

Arterial blood gases, pH and A-aDO2 analyses were not performed during the insult.

The RVP responded to the insult with hypertension. The peak RVP response occurred after the peak ICP which was at the completion of the injection; it then gradually returned to normal levels. The RVP "time to change", "time to peak" and "time to recover" for the artificial CSF group, are shown in tables 3 and 4. The "time to change" and "time to peak" were longer than these times for the MaBP, ICP and respiratory patterns. The "time to recover" was longer for the RVP than for the ICP or respiratory pattern and less than that for MaBP. The mean, maximum RVP response is also presented in table 3.

The post-insult Vt, RR and arterial blood gases, expressed as percentages of resting, are shown in tables 8 and 9. The actual pH, A-aDO2 and RVP values are also shown. For the 2 groups, the actual measured PaCO2 and PaO2 are shown graphically in figure 19, and A-aDO2 in figure 36.

The Vt of the artificial CSF group at CBF (5) was slightly above the resting level and that of the 1.67 ml/kg SAH group was more elevated although neither of these values was significantly greater than the control level. The RR of the artificial CSF group was not significantly different from the resting level; that of the 1.67 ml/kg SAH group was slightly decreased (ns).

The PaCO2 of the artificial CSF group was only slightly decreased at the fifth CBF determination; that of the 1.67 ml/kg SAH group was decreased to a greater degree but this was not statistically significant. The PaO2 of the artificial CSF group remained unchanged whereas that of the 1.67 ml/kg SAH group was lower than the resting value (ns).

The pH of both groups was increased at this flow, but not significantly different from resting values. The noted increases in pH in the 2 groups were not significantly different from each other, however, the 1.67 ml/kg group showed the greater increase.

The A-aDO2 values of both groups were significantly elevated at CBF (5) ($p<0.05$), with the increase of the 1.67 ml/kg group being significantly greater than that experienced by the artificial CSF group ($p<0.05$).

The RVP of the artificial CSF group returned to a level significantly lower than resting ($p<0.05$). This decrease, however, was only 3 mm Hg.

The Vt of the artificial CSF group remained elevated (ns) at CBF (6) but returned to normal by CBF (7) for the remainder of the studies. There were however, some Vt fluctuations but they were not statistically significant.

In the 1.67 ml/kg SAH group, the Vt returned to normal by CBF (6), but also demonstrated small fluctuations during the remainder of the experimental studies (ns).

The RR of the artificial CSF group remained normal for the duration of the studies although small increases at CBF (9,10) were noted. Respiratory rate in 1.67 ml/kg SAH group was also within normal limits during the following CBF determinations, but with small decreases during CBF (8,9). The relative changes in Vt and RR during the post-insult studies were not significantly different between the 2 groups.

The PaCO2 values for the artificial CSF group were normal at CBF (6,7,8), but decreased significantly during CBF (9) ($p<0.01$) and CBF (10) ($p<0.05$). The PaCO2 for the 1.67 ml/kg SAH group at CBF (6) was lower than resting (n.s.). The PaCO2 values for the remaining CBF determinations were normal, except for a non-significant decrease during CBF (10).

The PaO2 values in the artifical CSF group remained normal for the duration of the experimental studies. For the 1.67 ml/kg SAH group, PaO2 levels remained lower than resting up to and including CBF (8), after-wise they were normal. These decreases were statistically significant, and the lowest PaO2 value occurred at CBF (6) (figure 19(a)).

pH in the artificial CSF group remained above (n.s.) resting level during the post-insult CBF measurements. In the 1.67 ml/kg group pH remained slightly below resting levels during CBF (7,8,9,10) measurements. The changes seen in arterial blood gases and pH during the post-insult studies were not significantly different between the 2 groups.

A-aDO2 of the artificial CSF group was slightly elevated (ns) at CBF (6,7,8,9) and significantly so at CBF (10) ($p<0.01$). In the 1.67 ml/kg SAH group A-aDO2 remained elevated (ns) at CBF (6) and during the following CBF determinations. During these later flows A-aDO2 gradually decreased towards normal (fig. 36; tables 8 and 9). The A-aDO2 elevations of the 1.67 ml/kg SAH group tended to be greater than those of the artificial CSF group, but this was not significant.

RVP in the artificial CSF group at CBF (6) was normal, and remained so for the duration of the experimental studies.

The 1.67 ml/kg SAH group experienced greater respiratory abnormalities during and after the insult than did the artificial CSF group; larger changes in arterial blood gases and A-aDO2 values subsequent to the injection were also evident.

(c) Regional Cerebral Blood Flow and Cerebrovascular Resistance Responses.

rCBF and CVR values for the 2 groups during the pre-insult period are presented in table 2. No significant differences were seen in these parameters for each group.

Overall mean values for the rCBF and CVR are also in the table.

Tables 5 and 6 document the post-injection values of rCBF and CVR for the 2 groups; rCBF's expressed a percentage of normal, and CVR as actual values. The pre and post-insult rCBF values are presented graphically for the artificial CSF group and 1.67 ml/kg SAH group in figures 37 and 16 respectively. Figure 38 shows the pre and post-injection CVR values of the 2 groups.

Both of the groups experienced a significant decrease in rCBF at the CBF (5) ($p<0.05$). The decrease in rCBF in the 1.67 ml/kg SAH group was greater than that in the artificial CSF group; however, the rCBF decreases were not significant different from each other.

CVR in both groups showed an increase at CBF (5); only the artificial CSF group elevation was significantly greater than the resting level ($p<0.05$). However, the absolute value of the increase in CVR in the 1.67 ml/kg SAH group was greater than that in the artificial CSF group. These CVR increases were not significantly different from one another.

The artificial CSF group demonstrated an improvement in rCBF at CBF (6), but it still was lower (n.s.) than resting and it remained this way for the duration of the studies.

rCBF in the 1.67 ml/kg SAH group also showed some improvement at CBF (6). This rCBF level, as well as those of the following determinations were persisitently lower (n.s.) than normal. The decreases were greater in this group than in the artificial CSF group, but not significantly so.

CVR in the artificial CSF group remained slightly greater (n.s.) than resting throughout the remaining studies.

In the 1.67 ml/kg group, CVR recovered somewhat at CBF (6), but remained above normal levels (n.s.) for the duration of the investigation. These increases were larger than those of the artificial CSF group, but not significantly so.

The 1.67 ml/kg SAH group experienced larger decreases in rCBF and greater increases in CVR than did the artificial CSF group.

(d) Cerebral Angiography

The mean pre-insult IDICA diameters for both groups are presented in table 2. Post-injection IDICA calibres, expressed as a percentage of resting, are shown in tables 5,6. The actual pre and post-insult IDICA measurements are presented graphically in figures 16 and 37.

The cerebral angiograms in figures 39(a),(b),(c) are representative of pre and post-injection states of the artificial CSF group. Figures 25 (a),(b),(c) show cerebral angiograms representing these states in the 1.67 ml/kg SAH group.

No changes in angiographic cerebrovascular status occurred in the artificial CSF group in the post-insult period, as opposed to the persistent diffuse vasospasm experienced by the 1.67 ml/kg SAH group. The IDICA diameter of the artificial CSF group remained unchanged in both post-injection angiographic studies. In the 1.67 ml/kg SAH group, the IDICA diameter was significantly reduced at the first study ($p<0.01$), as well as at the second study ($p<0.05$).

(e) Neurological Examination

Neurological status of all experimental animals in the 4 SAH volume groups, the 2 SDH volume groups and the artificial CSF group was assessed at 5 hours and 20 hours post-insult. The grading system used, as described previously in Chapter II (Methods), was a 5 point scale (1-5), describing increasing neurological abnormalities, from normal (1) to moribund (5).

The mean grades at these observation periods for all groups are shown in table 16. In general, in the 4 SAH volume groups, the 1.0 and 1.33 ml/kg SAH animals fared better at both neurological examinations, than did the larger SAH volume groups (1.67, 2.0 ml/kg). Two animals died in each of the 2 lower volume groups between the 5 hour and the 20 hour observation periods. The remaining animals in these groups at 20 hours were neurologically normal. In the larger SAH volume groups, 2 animals in each group died before the 5 hour neurological examination period (grade), and the remainder were dead by 20 hours post-SAH.

In the SDH groups, the 1.67 ml/kg group showed minimal neurological deficit at the 5 hour examination, and the 2.0 ml/kg animals were normal. After 20 hours, the 1.67 ml/kg group animals were normal, and for the 2.0 ml/kg group, 1 animal was normal and the other was dead.

The artificial CSF group animals, in general were lethargic at the 5 hour observation period. By the 20 hour examination, 4 animals recovered and were neurologically normal. The remaining animal died of acute peritonitis between the 2 observation periods, and was not included in the 20 hour mean neurlogical grade for this group.

Animals perfused with glutaraldehyde, prior to the 20 hour examination, were sacrificed by this method during cardiovascular decompensation from which it was felt that there would be no recovery. These animals were considered grade 5.

(f) Pathological Examination of Brain

Examination of the dura by palpation, on removal of the ICP device, supplied us with information about the intracranial status at that point in time. The grading scale, as previously described in Chapter II (Methods), for the dura was; normal, slightly full, full and tight.

For the lower volume SAH groups (1.0, 1.33 ml/kg), the status of the dura ranged from normal to full. The dura was not found to be tight in any of these experimental animals.

In the 1.67 and 2.0 ml/kg SAH groups, the dura was tight in all cases, including both those dying acutely and those surviving the 5 hour observation period.

In the SDH groups, the dura examination ranged from normal to full.

Similarly, examination of the dura in the artificial CSF group showed it to range from normal to full.

The appearance at postmortem of an induced SAH is shown in figure 40.

At postmortem examination, the brains were removed and examined grossly. The examination scale used, as previously described in Chapter II (Methods), was normal, slightly swollen, swollen and bulging. In general, the brains of the experimental animals in the 2 lower volume SAH groups appeared slightly swollen. In 2 animals of the 1.33 ml/kg SAH group, the brains were swollen. In the higher volume SAH groups (1.67,2.0 ml/kg) the brains were swollen.

For the SDH groups, the appearances of the brains ranged from normal to slightly swollen.

In the artificial CSF group, the brains were generally normal, except for 2 of them, which were slightly swollen.

Table 17 shows the mean weight of the brains immediately following their removal from the cranium, for the 4 SAH volume groups and the artificial CSF group (brains of the SDH group animals were not weighted). These mean weights are also expressed as brain weight in grams per kilogram body weight in the same table. There were no significant differences in the mean "wet" brain weights or in the mean brain weight/body weight values.

Following weighing and photography, the brains were immersed in formaldehyde for at least 2 weeks, and were then reweighed and sectioned.

The brain weights following formaldehyde immersion was greater than the respective fresh "wet" brain weights. The mean increases are shown in table 17. The numerals in parenthesis in the table represent the number of animals (brains) used in the calculations. Those animals not included, either underwent glutaraldehyde perfusion, or the brains were not weighed.

Three brains from this study were examined histologically; 1 from the 1.67 ml/kg SAH group and 2 from the 2.0 ml/kg SAH group. These brains in general showed diffuse edema, and multifocal areas of ischemia and infarction.

Intraventricular hemorrhage was present in some of the animals of the 4 SAH volume groups under study: 4 in 1.0 ml/kg; 2 in 1.33 ml/kg; 2 in 1.67 ml/kg; 3 in 2.0 ml/kg. Venticular dilatation was present in 3 animals, and they all had intraventricular blood. There was 1 in each of the 3 larger volume groups (1.33, 1.67, 2.0 ml/kg).

The artificial CSF group animals did not demonstrate either intraventricular blood or ventricular dilatation.

Of the 4 acutely dying animals, the 2 from the 1.67 ml/kg SAH group did not have intraventricular blood, whereas the 2 from the 2.0 ml/kg SAH group did. None of the these 4 animals demonstrated ventricular dilatation.

(g) Electron Microscopy

Electron microscopic examination of cerebral vessels was carried out in the animals perfused with glutaraldehyde. The vessels studied were IDICA, MCA, PPA and DPA. The sites examined in the 3 former vessels were those measured at angiography.

The specimens were examined mainly for vasospasm, evidenced by in folding of the intima and contraction of the intima and media muscle cells.

A 4 point grading system (0,1,2,3) was used for describing the undulations and infolding of the intima. Higher grades documented greater degrees of vasospasm. Using this system, 0 was considered to be normal, and documented a completely level intima. A value of 1 was used to describe slight undulations of the lumen-endothelial border. This grade was not considered pathological, because in most cases, the slight undulations present were caused by an underlying intimal muscle cell nucleus, or segmentaaly thick areas of the intima or internal elastic membrane (fig. 41).

Grades 2 and 3 were considered as pathological, and describe increasing degrees of vasospasm. In these grades, there was undulation of increasing severity of both the luminal and adventitial surfaces of the intima. At these higher grades of intimal change, the underlying media musculature, as well as that of the intimal layer, was contracted.

Table 18 shows the electron microscopic evaluation of cerebral vessel intimal changes of the individual animals studies in the SAH volume groups, the 1.67 ml/kg SDH group and the artificial CSF group. None of the experimental animals of the 2.0 ml/kg SAH or SDH groups were examined in this fashion. Tissue samples excluded from the table were either not examined, or were not interpretable because of poor preparation.

In the 1.0 and 1.33 ml/kg SAH groups, the animals were perfused following the 20 hour observation period. In these lower volume groups, the cerebral vessels studied were normal, ranging from grades 0-1. Figures 42(a),(b) are representative of the appearance of the intima (grade 1) and the media musculature of these vessels. There is very minimal undulation of the intima. The muscle cells are normal; they are long, with smooth borders, and their nuclei are long and slender.

In the larger SAH volume groups, 3 animals of the 1.67 ml/kg group were perfused with glutaraldehyde at the point of complete cardiovascular collapse, just prior to death. In 2 of these animals, cerebral angiography studies were performed immediately before perfusion. Both of these showed marked cerebral vasospasm.

Figures 43(a),(b) are cerebral angiograms of 1 of these animals. The pre-SAH angiogram demonstrates normal cerebral vessels, and the angiogram performed prior to the perfusion shows cerebral vasospasm.

In the 1.67 ml/kg SAH group, the IDICA and PPA consistently demonstrated marked intimal undulation and infolding, and the MCA and DPA vessels ranged from normal to grade 3. Figures 44(a),(b), show the appearance of marked vasospasm (grade 3) seen in this group. These cerebral vessels are from the same animal as the previously shown cerebral angiograms (figs. 43(a),(b)), and the sites from which the samples were taken are illustrated on the angiogram that was performed just prior to the perfusion (fig. 43(b)). Severe infolding and undulation of the intima is present, along with marked muscular contraction of the media. The contracted muscle cells are shortened and have become fat; the borders have a serrated appearance; their nuclei are bulky and kinked (fig. 44(b)). This picture is markedly different from that of the flat intima and long fine slender muscle cells of normal vessels.

In the 1.67 ml/kg SDH group, the E.M. examination of the vessels showed grades 0-1. The intima was slightly undulated at the luminal surface only, and was not thrown into folds. (fig. 45(a)). The media musculature appeared normal. The muscle cells and their nuclei were fine, long and slender. The intimal muscle in figure 45(b) is not contracted, and is normal.

The cerebral vessels of the artificial CSF group are normal, and range from grades 0-1. Figure 46(a) shows the pre-insult cerebral angiogram, and figure 46(b) the post-insult cerebral angiogram prior to glutaraldehyde perfusion of the animal whose cerebral vessels are presented in figure 41 & 47(a),(b). The area from which the E.M. samples were taken are shown on the latter angiogram. No cerebral vasospasm is present on this angiogram. The minimal intimal undulations at the luminal surface seen in figure 47(a) are due to underlying intimal muscle cells. The intima is seen to be level in figure 41. Media musculature is normal (fig. 47(b)).

(h) Pulmonary Pathology

Of the 5 animals in this group, 4 were sacrificed by glutaraldehyde perfusion. The weights of the lungs of these 4 animals were not recorded because they were perfused with glutaraldehyde and the weights would not be interpretable compared to those of the lungs of animals not perfused. Histological examination using H and E stain revealed the lung tissue in these animals to be normal. Figure 48 documents the appearance of the lung tissue representing this group under low power magnification. The fifth animal in this group died from acute peritonitis. The post-mortem weight of it's lungs together was 26.2 gms. Histologically there was mild intra-alveolar and interstitial edema.

II. STUDY B: TREATMENT OF INDUCED SAH AND SDH WITH SIMULTANEOUS INTRAVENOUS INFUSIONS OF SODIUM NITROPRUSSIDE AND PHENYLEPHRINE IN THE SPONTANEOUSLY BREATHING PRIMATE.

(i) Treatment of Induced SAH With Simultaneous Infusions of Sodium Nitroprusside and Phenylephrine in the Spontaneously Breathing Primate.

(a) Cardiovascular and Intracranial Pressure Responses.

This section deals with the results of the SAH treated group. Those of the 1.67 ml/kg SAH and artificial CSF groups are also presented for comparisons and contrasts.

The mean weights of the monkeys in these groups are shown in table 1. There were no significant differences between these weights.

Means, and SEM, for MaBP, HR, ICP and CPP during each pre-insult CBF determination for the 3 groups are presented in table 19. Within the SAH treated (SAHRx) group, the MaBP of CBF (4) was significantly greater than that of CBF (2) ($p<0.05$). The actual difference was 9 mm Hg. There were no other significant differences in the pre-insult MaBP levels, nor were there any in the HR or CPP values during this period. The overall means for these parameters are also in table 19. The ICP was first measured during CBF (4).

Typical cardiovascular, ICP, respiratory pattern and RVP responses to an induced SAH of 1.67 ml/kg are shown in figure 49. As occurred in the previously discussed groups, the first experimental parameter to change was the ICP, followed in sequence by MaBP, respiratory pattern, HR and RVP. The hemorrhage caused increases in ICP, MaBP and RVP, bradycardia and other arrythmias, and respiratory pattern abnormalities.

The initial response of MaBP to the hemorrhage in 2 of the 8 animals was hypotension with a mean decrease of 13±5 mm Hg. The duration of the hypotension was 10±5 seconds. These values are not significantly different from those of the 1.67 ml/kg SAH and artificial CSF groups, but both the decreases and the time tended to be less than occurring in these 2 groups. The hypotension in these 2 animals was followed by hypertension, which was the initial response of the remaining 6 animals of the SAHRx group. Following this, the MaBP of all animals gradually returned to normal levels.

The times, in these 3 experimental groups, for the "MaBP to change", "MaBP to peak" and "MaBP to recover to normal" are shown in tables 20 and 21. No statistically significant differences were found in these times for the 3 groups. As was the case with the 1.67 ml/kg SAH group, the time for the "MaBP to peak" tended to be longer than that of the artificial CSF group.

The maximum MaBP responses for the groups are given in table 20. There were no significant differences between these values. That of the SAHRx group tended to be greater than the peak values of the other 2 groups.

The responses of HR to the insult in the SAHRx group was bradycardia occurring 34±8 seconds after the start of the hemorrhage. Sinus bradycardia was present in 2 animals, and junctional rhythm bradycaria in 3. The bradycardia of the 3 remaining animals was of unknown etiology. Four of these 8 animals also demonstrated other arrythmias consisting of PVB's, PVB bigeminy, premature atrial contractions (PAC's), supraventricular beats, idioventricular rhythm and ventricular tachycardia. One animal showed ST segment elevation, and 5 animals had T wave changes of flattening, inversion and peaked T waves. Figure 50 shows some of the arrythmias and EKG pattern irregularities seen in this group.

By the fifth CBF determination, 9±1 minutes post-insult, the EKG and HR returned to normal in 6 of 8 animals. In the remaining 2, the T wave remained inverted until CBF (7) in 1 and CBF (8) in the other. One animal developed bradycardia and an upright T wave during cardiovascular decompensation just prior to death and CBF (9).

The HR values for the 3 groups at peak ICP and peak MaBP are shown in table 21. There are no significant differences between these 2 rates of the SAHRx group, and they tended to be lower than the values of the other groups.

Subsequent to the SAH, the mean HR was slowest at 74±7 seconds post-insult initiation, at a value of 84±9 beats/minute. This bradycardia occurred after the peak MaBP. These values and findings are similar to those of the other 2 groups.

The mean times for the "ICP to change" and the "ICP to peak" for the 3 groups are shown in table 20. There were no significant differences in these times between the 3 groups.

The peak ICP responses are given in table 20. The maximum ICP value subsequent to the insult for the SAHRx group was significantly greater than that of the 1.67 ml/kg SAH group ($p<0.05$) and only tended to be greater than that of the artificial CSF group.

After the peak, the ICP fell rapidly at first and then more gradually to a steady state value. In 5 of the animals in the SAHRx group, the ICP returned to normal levels, and in 3 the ICP remained elevated, 2 at 18 mm Hg and 1 at 28 mm Hg. The "half-time ICP decay" for the groups are shown in table 21. These times are not significantly different, but those for the SAHRx and 1.67 ml/kg SAH group are longer than that of the artificial CSF group.

The times for the "ICP to recover" to a post-insult steady state level are shown in table 21. This time for the SAHRx group was not different from that of the 1.67 ml/kg SAH group, and the times for both these groups were significantly greater than that of the artificial CSF group ($p<0.05$).

The $\overline{\text{CPP}}$ and $\overline{\text{CPP1}}$ levels for all 3 groups are presented in table 21, and they are not significantly different between the 3 groups. The $\overline{\text{CPP}}$ of the SAHRx group tended to be lower than those of the other 2 groups. The $\overline{\text{CPP1}}$ of the SAHRx group tended to be lower than those of the other groups.

The MaBP, HR, ICP and CPP values for the 3 groups during the post-insult CBF determinations are shown in table 22. The pre and post-insult CPP values are depicted in figures 16,37 and 51. For the SAHRx group, the MaBP at CBF (5) was significantly lower than normal ($p<0.01$). The MaBP of the 1.67 ml/kg SAH group tended to be lower than resting and that of the artificial CSF group was unchanged. The MaBP decreases in the 2 SAH groups were not significantly different from one another.

As was the case with the 1.67 ml/kg SAH and artificial CSF groups, EKG and HR of the SAHRx group were normal at CBF (5) (except for the previously discussed T wave changes).

Mean ICP values of the 3 groups recovered to within normal limits by this flow determination. Three animals in the SAHRx group, as previously described had elevated ICP steady state levels. These persisted during CBF (5), 2 at 18 mm Hg and 1 at 28 mm Hg. The ICP device malfunctioned in this latter experimental animal in the period during the fifth and sixth CBF determinations, and did not function correctly for the duration of the studies. In the other 2 animals, the ICP returned to normal by CBF (6) (50±3 minutes post-insult).

The CPP at CBF (5) for the SAHRx group was significantly lower than resting ($p<0.01$), as was that of the 1.67 ml/kg SAH group ($p<0.05$). The artificial CSF group CPP was not different than normal. The respective decreases in CPP for the SAH groups were not significantly different from one another.

After the fifth CBF determination, treatment was initiated in the SAHRx group. The mean time required to institute an adequate treatment regime (as described in the previous chapter on METHODS) was approximately 25 minutes. With this delay, the sixth rCBF determination in the SAHRx group corresponded in time with the seventh of the other 2 groups. Comparisons and contrasts of the various physiological parameters of these 3 groups are thus carried out in this staggered fashion, as documented in table 22.

At CBF (6), the MaBP of the SAHRx group was significantly lower than resting ($p<0.01$). The MaBP values of the other 2 groups at CBF (7) were lower, but not significantly, than normal. The decrease in MaBP of the SAHRx group was greater than those of the other 2 groups, but only significantly greater than that of the 1.67 ml/kg

SAH group ($p<0.05$).

The HR of the SAHRx group was only slightly greater than resting, and those of the other 2 groups were essentially unchanged.

Mean ICP of the groups was normal at this point in time. In the SAHRx group, as in the 1.67 ml/kg SAH group, the ICP of only 1 animal remained elevated; 28 mm Hg in the former and 20 mm Hg in the latter.

At this flow, the CPP of the SAHRx group was significantly lower than normal ($p<0.01$). The corresponding CPP value for the 1.67 ml/kg SAH group was lower than normal, but not significantly, and that of the artificial CSF group was unchanged. The decreases experienced by the 2 SAH groups were not significantly different.

During the CBF (7,8,9) for the SAHRx group, which correspond to CBF (8,9,10) of the other 2 groups, the MaBP remained significantly lower than resting ($p<0.01$). For the other 2 groups, MaBP remained lower than resting, but not significantly, in the 1.67 ml/kg SAH group for the duration of the studies, whereas that of the artificial CSF group remained normal, except for a slight non-significant decrease during CBF (7). Decreases in MaBP experienced by the 2 SAH groups at corresponding times, were significantly greater for the SAHRx group during CBF (7) and CBF (8) ($p<0.05$). At CBF (9), of the treated group, there were no significant differences in the MaBP decreases of the 2 groups.

The HR of the SAHRx group remained normal for CBF (7,8,9), with a slight non-significant increase at CBF (8). During the last 3 flows of the 1.67 ml/kg SAH group, HR values were elevated, but not significantly, above resting In the artificial CSF group HR of the final 2 CBF determinations were significantly greater than resting ($p<0.05$). The relative HR changes in the 3 groups were not significantly different.

The mean ICP of the SAHRx group was normal at CBF (7) and remained within resting levels for the duration of the studies. There was however a non-significant increase in mean ICP in this group at CBF (8), to 17±4 mm Hg. This increase reflects the increases in ICP levels at this flow determination in 4 of the 7 surviving animals. (ICP device malfunction in 1 animal, and the ICP remained normal in the others). Two of these 4 animals with elevated ICP had normal ICP values at CBF (9), and all animals had normal ICP levels by CBF (10).

The 2 animals dying acutely in this substudy did not have elevated ICP values prior to death. Similarly the 2 animals dying in the 1.67 ml/kg SAH group did not have increased ICP. However, the 2 animals dying acutely in the SAHRx group were the same 2 animals that had persistent ICP elevations (both at 18 mm Hg) during CBF (5), with a subsequent return to normal level by the CBF (6) (50±3 minutes post-SAH).

The CPP levels for the SAHRx, group remained significantly below normal levels for CBF (7,8,9) inclusive ($p<0.01$) (fig. 51; table 22). For the 1.67 ml/kg SAH group the CPP remained persistently, but not significantly below resting. In the artificial CSF group, these values were within normal limits, if not slightly elevated (except CBF (7) where it was normal). The corresponding decreases in CPP for the SAH groups were not significantly different from each other.

The tenth rCBF determination was the final flow before the treatment regime was discontinued. The MaBP remained significantly below resting ($p<0.01$). The ICP was normal. There was an non-significant elevation of HR at this flow. As was the case with the MaBP, the CPP remained significantly lower than resting ($p<0.05$).

CBF (11) was determined at least 10-15 minutes after the cessation of the treatment. The MaBP and CPP returned to normal resting levels. The HR was slightly but not significantly elevated. Table 22 shows the ICP to remain normal, but slightly decreased compared to its level during the treatment. This decrease was not found to be significant.

Two animals died acutely in the SAHRx group, 1 at 94 minutes (20 minutes after CBF (7)) and the other at 149 minutes (10 minutes after CBF (9)) post-SAH. MaBP, ICP and CPP in these animals measured at the flow prior to death were not significantly different from their respective resting levels. CPP in both animals was 70 mm Hg.

As noted previously, 2 animals died acutely in the 1.67 ml/kg group; 1 underwent cardiovascular decompensation during CBF (5). MaBP was low and the ICP normal, which resulted in a CPP of 32 mm Hg. The second animal died 18 minutes (10 minutes after CBF (5)) post-SAH. MaBP, ICP and CPP levels in this animal were normal. The CPP was 72 mm Hg.

The responses of MaBP, HR, ICP and CPP to the insult of the SAHRx group were similar to those of the 1.67 ml/kg SAH group, and were more marked than those of the artificial CSF group. With the institution of the treatment regime, MaBP and CPP of the SAHRx group were lower than those at the other 2 groups. On cessation of the treatment program MaBP and CPP returned to normal at CBF (11).

(b) Respiratory Pattern, Arterial Blood Gas, Alveolar-Arterial Oxygen Difference and Right Ventircular Pressure Changes

The pre-insult respiratory pattern parameters (Vt and RR), arterial blood gases, pH, A-aDO2 and RVP for the 3 groups are shown in table 23. There were no significant differences found between Vt, RR, PaO2, pH and A-aDO2 measurements during the 4 pre-SAH flows of the SAHRx group, except for A-aDO2 at CBF (4) being significantly greater than that at CBF (2) ($p<0.05$), and PaCO2 of CBF (4) being significantly less than that of CBF (3) ($p<0.05$), CBF (2) ($p<0.01$), and CBF (1) ($p<0.05$). The differences range from 1-3 mm Hg. For RVP, that of CBF (2) was significantly greater than that of CBF (4) ($p<0.05$). The difference was only 5 mm Hg.

A discussion of these physiological parameters during the pre-insult period for the 1.67 ml/kg SAH and artificial CSF groups has been presented in the previous section. The overall means for these parameters of the 3 groups are also shown in table 23.

As was the case with the previously discussed groups, the initial response of the respiratory pattern to the insult was quite variable, and no specific patterns were demonstrated. In the SAHRx group, as in the other 2 groups, the respiratory pattern changes progressed to varying periods of apnea in all animals.

The mean times for the respiratory pattern to change from the onset of the insult in these groups are shown in table 20. There were no significant differences in these times for the SAH groups, but that of the artificial CSF group was significantly longer than that of the SAHRx group ($p<0.01$).

Mean durations of the apneic episodes for the 3 groups are shown in table 20. This duration for the SAHRx group was significantly longer than that of the artificial CSF group ($p<0.05$) and significantly shorter than that of the 1.67 ml/kg SAH group ($p<0.01$).

The mean times for "respiration to recover" are represented in table 21, and this time for the SAHRx group (116±12 seconds) is significantly shorter than that of the 1.67 ml/kg SAH group ($p<0.05$) and significantly longer than that of the artificial CSF group ($p<0.01$).

Arterial blood gases, pH and A-aDO2 analyses were not performed during the insult.

As was the case with the RVP of the artificial CSF group, that of the SAHRx group responded to the insult with hypertension, which gradually returned to normal after the injection. The RVP "time to change". "time to peak" and "time to recover" for the SAHRx and artificial CSF groups are recorded in tables 20 and 21. The "time to change" for both these groups were similar. The time for RVP of the SAHRx group to peak was longer than that of the artificial CSF group (ns), and so was the "time to recover". The "time to change" and "time to peak" were longer than these times for MaBP and ICP in both groups. It was also noted that the RVP "time to change" for these groups was longer than this time for the respiratory pattern. The "time to recover" for RVP of the SAHRx group was longer than recovery time for respiration, but shorter than this time for MaBP and ICP. In the artificial CSF group, RVP "time to recover" was longer than for ICP and respiration recovery time and shorter than the period for MaBP to recover.

The peak RVP responses are shown in table 20 and they are not significantly different.

The post-insult Vt, RR and arterial blood gases, expressed as percentages of resting are shown in table 24. The actual pH, A-aDO2 and RVP values are also shown. The actual measured PaCO2 and PaO2 for the 3 groups are shown graphically in figure 52, and A-aDO2 in figure 53.

At CBF (5) the Vt of the SAHRx group was slightly greater (ns) than resting, and the RR less (ns) than control. For the 1.67 ml/kg SAH group there was a greater increase in Vt (ns) above resting, and RR was less (ns) than normal. The artificial CSF group Vt demonstrated a slight non-significant increase and RR remained unchanged. The various increases in Vt of the 3 groups were not significantly different from each other, and neither were the slight decreases in the RR of the SAH groups.

There was a significant decrease in PaCO2 of the SAHRx group at CBF (5) from resting ($p<0.05$). In the 1.67 ml/kg SAH group, PaCO2 was less (ns) than normal, and there was only a slight non-significant decrease of the PaCO2 of the artificial CSF group. These relative decreases were not significantly different from one another.

The PaO2 of the SAHRx and artificial CSF groups were unchanged at CBF (5) and that of the 1.67 ml/kg SAH group was lower (ns) than the resting value.

All 3 groups showed elevations of A-aDO2 at CBF (5). which was significant for the 1.67 ml/kg SAH and artificial CSF groups ($p<0.05$). The A-aDO2 elevations of the artificial CSF and SAHRx groups were similar, and that of the 1.67 ml/kg SAH group was significantly greater than this value for the SAHRx group ($p<0.05$).

The RVP of the SAHRx group returned to normal at CBF (5) and that of the artificial CSF group was significantly lower than resting at this flow ($p<0.05$).

As previously discussed, because of the time necessary to institute the treatment regime, CBF (6) of the SAHRx group corresponds in time to CBF (7) of the 1.67 ml/kg and artificial CSF groups. Thus, the physiological parameters discussed in this section for CBF (6,7,8,9) of the SAHRx group will be compared with those of the 1.67 ml/kg SAH and artificial CSF groups at corresponding times, CBF (7,8,9,10), table 24.

The Vt of the SAHRx group showed non-significant fluctuations throughout the studies, consisting of increases at CBF (6,9), a decrease at CBF (7) and no change at CBF (8). For the 1.67 ml/kg SAH group, the Vt was slightly decreased (ns) at CBF (7) and slightly increased (ns) at CBF (8,9,10). In the artificial CSF group Vt was low at CBF (8), increased at CBF (10) and unchanged at CBF (7,9).

The SAHRx group experienced no changes from resting in RR. In the 1.67 ml/kg SAH group, RR remained less (ns) than resting for the duration of the studies. The artificial CSF group showed no changes in RR during CBF (7) and slight increases (ns) for the duration of the investigation. The various changes exhibited by these groups in Vt and in RR were not significantly different from each other.

In the SAHRx group, PaCO2 remained less than resting for CBF (6,7,8,9) but only significantly at CBF (8) ($p<0.01$) and CBF (9) ($p<0.05$). PaCO2 of the other 2 groups was less (ns) than resting for the duration of the studies. The decreases in PaCO2 of the SAHRx group appeared to be greater than those of the other 2 groups, but these changes were not significantly different from one another.

PaO2 of the SAHRx group was slightly decreased (ns) for CBF (6,7,8,9). For the 1.67 ml/kg SAH group PaO2 remained low (ns) for CBF (7,8,9) and normal at CBF (10). The artificial CSF group PaO2 was normal for CBF (7,8,9) and low (ns) at CBF (10). PaO2 decreases appeared to be greater for the 1.67 ml/kg SAH group, but there were no significant differences in the PaO2 changes between the 3 groups.

The pH levels remained elevated (ns) in the SAHRx group for CBF (6,7,8,9), as did that of the artificial CSF group (ns) for CBF (7,8,9,10). For the 1.67 ml/kg SAH group, the pH remained low (ns) for the duration of the studies. The various pH changes exhibited by the 3 groups were not significantly different from each other.

The A-aDO2 of the SAHRx group was elevated during CBF (6,7,8,9), and significantly so at CBF (9) ($p<0.05$). The A-aDO2 for the other 2 groups were elevated above resting during CBF (7,8,9,10) and significantly so at CBF (10) for the artificial CSF group ($p<0.01$) (fig. 53; table 24). The corresponding elevations in A-aDO2 at these CBF determinations were not significantly different between the 3 groups. In general, however, the A-aDO2 elevations of the 1.67 ml/kg SAH group tended to be greater than those of the SAHRx group, and these latter tended to be greater than the A-aDO2 changes of the artificial CSF group.

The RVP of the SAHRx group was lower than resting at CBF (6,7,8,9), and this difference was significant at CBF (6) ($p<0.05$) and at CBF (7) ($p<0.05$). The differences were small, and the maximum was 6 mm Hg. In the artificial CSF group, RVP was normal for the duration of the studies. The relative changes in RVP of these 2 groups were not significantly different.

During CBF (10) of the SAHRx group, prior to the discontinuation of the treatment, Vt was normal and RR was slightly decreased (ns). PaCO2 was significantly lower than resting ($p<0.01$) and PaO2 was slightly decreased (ns), pH remained elevated (ns). A-aDO2 was elevated (ns) at this CBF determination and RVP was slightly decreased (ns).

After cessation of the treatment regime, at CBF (11), both Vt and RR were elevated (ns). PaCO2 was significantly decreased ($p<0.05$). PaO2 was unchanged and pH remained elevated (ns.) A-aDO2 was greater than resting (ns) and RVP was normal.

In general, we found, in the same SAHRx group, that those animals experiencing a longer duration of RVP elevation subsequent to the insult showed a greater decrease in PaO2 and larger increase in A-aDO2 post-SAH.

Of the 2 acutely dying animals in the SAHRx group, 1 had a larger increase in A-aDO2 and a greater decrease in PaO2 compared to the surviving animals (fig. 53(b)). This same finding has been described previously as occurring in those acutely dying animals in the 1.67 ml/kg SAH group.

(c) Regional Cerebral Blood Flow and Cerebrovascular Resistance Responses.

rCBF and CVR for the 3 groups during the pre-insult CBF determinations are shown in table 19. No significant differences were seen in these parameters within each group. The overall means for rCBF and CVR for CBF (1,2,3,4) for each group are also shown in table 19.

Table 22 documents the post-injection values of rCBF expressed as a percentage of normal, and of CVR as actual measurements for all 3 groups. Actual pre and post-insult rCBF values are graphically presented in figures 16,37,51. The mean CVR pre and post-insult for all 3, including all animals are graphically represented in figure 54. The mean CVR for those animals surviving the 5 hour observation period in the SAHRx and 1.67 ml/kg SAH groups are shown in figures 20(b) and 54(b), along with the CVR values of the animals dying acutely.

The initial response of rCBF of the SAHRx group measured at CBF (5) was a significant decrease to 20±2 ml/100 gm/minute ($p<0.01$). The 1.67 ml/kg SAH group also experienced a significant decrease in rCBF to 18±2 ml/100 gm/minute ($p<0.05$). The artificial CSF group demonstrated a significant decrease to 51±4 ml/100 gm/minute ($p<0.05$). The rCBF decrease of the SAHRx group was significantly greater than that of the artificial CSF group ($p<0.01$), and not significantly different from that of the 1.67 ml/kg SAH group. The rCBF decrease of the 1.67 ml/kg SAH group was greater, but not significantly different, than that of the artificial CSF group.

The CVR of the SAHRx group increased significantly at CBF (5) ($p<0.01$), as did that of the artificial CSF group ($p<0.05$). The 1.67 ml/kg SAH group experienced a non-significant increase in CVR at this flow.

The increase in CVR of the SAHRx group was significantly greater than the increase noted in the artificial CSF group ($p<0.01$), and not significantly different than that experienced by the 1.67 ml/kg SAH group. The increases in CVR of the 1.67 ml/kg SAH and artificial CSF groups were not significantly different from each other.

The following deals with rCBF and CVR in the SAHRx group at CBF (6,7,8,9) and those of the other 2 groups at CBF (7,8,9,10). The rCBF of the SAHRx remained significantly lower than resting for CBF (6,7,8,9) ($p<0.01$). In the 1.67 ml/kg SAH group it remained lower (ns) than normal for the duration of the studies. The rCBF of the artificial CSF group was slightly lower (ns) than resting for the remaining investigations. Decreases in rCBF of the SAHRx group were slightly greater (ns) than those of the 1.67 ml/kg SAH group. They were also greater (ns) than those of the artificial CSF group. rCBF decreases of the 1.67 ml/kg SAH group were greater (ns) than those of the artificial CSF group.

The 2 animals dying acutely in the SAHRx group had greater initial decreases in rCBF subsequent to the SAH (CBF (5)) than did the survivors, both to 16±2 ml/100 gm/minute. These rCBF values represent 29% and 55% of their resting levels. The rCBF of these animals remained lower than the group mean, until their demise. This sequence of events was similar to that occurring with the acutely dying animals in the 1.67 ml/kg SAH group.

The CVR of the SAHRx group remained elevated (ns) for CBF (6,7,8,9). That of the 1.67 ml/kg SAH group was elevated for the duration of the studies, and was significantly so only at CBF (9) ($p<0.05$). In the artificial CSF group, CVR was slightly greater (ns) than resting for the remaining investigations. The various increases in CVR experienced by the 3 groups during the corresponding flows following CBF (5) were not significantly different from each other, although CVR of the 2 SAH groups tended to be greater than that of the artificial CSF group.

Figure 54(b) shows graphically the CVR of the acutely dying animals as well as that of those surviving in the SAHRx group. With the CVR of the animals that died removed from the mean of the group, it is noted that the CVR increase during CBF (6,7,8,9) was still slightly greater (ns) than resting, but not as large as when they were included. One animal of this group that died acutely had a large increase in CVR at CBF (5) to 3.13 and it remained elevated until death (CBF (6,7)). The CVR of the other mortality in the group experienced a small increase at in CVR at CBF (5), that remained slightly above resting at CBF (6,7) and then demonstrated further increases at CBF (8,9), after which it died. These latter increases were greater than the mean CVR of the survivors at these flows.

Similarly, the animal that died after CBF (5) in the

1.67 ml/kg SAH group had a large increase in CVR to 5.14 at this flow.

The rCBF and CVR changes subsequent to the insult for the SAHRx and 1.67 ml/kg SAH groups were greater than those of the artificial CSF group. The responses of these parameters in the 2 SAH groups were similar.

Those animals that died acutely in the 2 SAH groups had greater decreases in rCBF and greater increases in CVR than those surviving the experimental studies.

(d) Cerebral Angiography

Angiography in the treatment series was performed in the same sequence and at the same post-insult times as the SAH volume and artificial CSF groups. A third post-injection cerebral angiography study was performed immediately on completion of CBF (11). As in the previous study, the data of IDICA measurement will be presented. In general, the other measured vessels (C1, MCA and CA) responded in similar fashion as the IDICA.

The mean pre-insult IDICA diameters for the 3 groups are shown in table 19. The post-injection diameters as percentages of normal are in table 22. Figures 16,37 and 51 demonstrated graphically the pre and post-insult IDICA measurements for the 3 groups. Representative angiograms pre and post-insult of these 3 groups are shown in figures

25(a),(b),(c), 39(a),(b),(c), and 55(a),(b),(c),(d).

The initial response to the SAH in the SAHRx group was diffuse cerebral vasospasm. This was also the case with the 1.67 ml/kg SAH group. The cerebrovascular status, post-insult of the artificial CSF group appeared normal.

Mean IDICA diameter of the SAHRx group on the first post-SAH determination was significantly lower than resting ($p<0.01$), as was that of the 1.67 ml/kf SAH group ($p<0.01$). The mean IDICA caliber of the artificial CSF group was unchanged. There was no difference in the degree of IDICA narrowing between the 2 SAH groups.

On the second set of cerebral angiograms of the SAHRx group performed after CBF (10) with treatment still in progress, cerebral vasospasm had abated somewhat, but was still present. This again is similar to the sequence of events in the 1.67 ml/kg SAH group. The cerebrovasculature of the artificial CSF group appeared normal.

The IDICA diameter, at this cerebral angiography sitting, for the SAHRx group recovered slightly, but still remained significantly below resting ($p<0.05$), as was the case with that of the 1.67 ml/kg SAH group. The IDICA caliber in the artificial CSF group was normal. There was no difference in the degree of spasm of the 2 SAH groups.

The cerebral angiograms performed following treatment discontinuation (after CBF (11)) revealed that the vasospasm had improved, but it was still present. The IDICA diameter showed more recovery but remained less (ns) than normal.

(e) Pulmonary Pathology

One animal in this study was sacrificed by gutaraldehyde perfusion. The mean postmortem weight of both lungs together of the remaining 7 animals was 25±3.0 gm. On gross examination of the lungs, 3 animals had a normal appearance, 3 had diffuse small petechial hemorrages, and there were larger hemorrhagic areas in the final animal. Microscopic examination revealed the presence of mild to moderate intra-alveolar and interstitial edema in 4 of the animals. Three animals had mild to moderate intra-alveolar edema only. Intra-alveolar hemorrhage was present in 2 animals, 1 with intra-alveolar and interstitial edema and the other with intra-alveolar edema. Figure 56 depicts the appearance of moderate intra-alveolar and interstitial edema. Proteinaceous fluid is present in the interstices and in the alveoli. The pulmonary tissue of the remaining animal was a poor preparation and was unable to be accurately interpreted.

Of the 2 animals dying acutely, 1 was perfused with glutaraldehyde and had moderate intra-alveolar edema. The lungs of the other acute mortality weighed 17.7 gm which is not different than the mean or from the weights of the lungs of the surviving animals in this group. Histological examination of these lungs showed mild intra-alveolar and interstitial edema. The appearance of these lungs did not differ from that of the surviving animals.

There were 4 animals in the treatment series, STUDY B that did not recover from the apnea resulting from the insult. Two of these animals received 1.67 ml/kg and 2 2.0 ml/kg.

Of the 2.0 ml/kg animals the weights of the lungs were 40.8 gm and 20.5 gm. In the former, the gross examination of the lungs revealed several diffuse hemorrhagic areas and hemorrhagic fluid present in the respiratory tree. Histological examination showed moderate intra-alveolar edema and mild interstitial edema, both with hemorrhagic components. The other lungs had a normal gross appearance and microscopically there was mild intra-alveolar hemorrhage and mild interstitial edema. Figure 57 shows the appearance of intra-alveolar hemorrhagic edema.

Concerning the other 2 animals, one was perfused with glutaraldehyde and the pulmonary tissue was not interpretable. For the remaining animal, the lungs appeared grossly normal and weighed 19.1 gm. The histological appearance consisted of very mild interstitial edema and mild intra-alveolar edema in 1 lung and the other lung was normal.

In the treatment series (STUDY B) 6 animals received an intracerebral (IC) hemorrhage. The lungs of these animals were removed and examined. Four of these animals were perfused with glutaraldehyde. The volume of SAH for these 4 was 1.67 ml/kg. The weights of the lungs of the remaining 2 animals were 27.9 gm and 13.9 gm, and the SAH volume was 2.0 ml/kg. They were of normal gross appearance. Microscopically there was very mild to mild intra-alveolar and interstitial edema present. Of the remaining 4 animals, the lungs of 2 of them showed mild to moderate intra-alveolar edema, 1 had intra-alveolar hemorrage and the pulmonary tissue of the final animal was a poor preparation and not interpretable. Figure 58 depicts the appearance of moderate intra-alveolar edema seen in this group.

(ii) Treatment Of Induced SDH With Simultaneous Infusions Of Sodium Nitroprusside And Phenylephrine In The Spontaneously Breathing Primate.

(a) Cardiovascular and Intracranial Pressure Responses.

This section deals with the SDH treated (SDHRx) group. The results of the SAHRx group will be presented for comparisons.

The mean weight of the experimental animals in the SDHRx group was 3.0±0.2 kg and is shown in table 1. It is not significantly different from the weights of the other groups.

Means, and SEM, for MaBP, HR, ICP and CPP during the pre-insult pericd are presented in table 25. Within the SDHRx group there were no significant differences in MaBP, in HR or in CPP measured during the 4 pre-hemorrhage CBF determinations. The overall means for these parameters are also shown in table 25. The ICP was first measured at CBF (4).

Typical cardiovascular, ICP, respiratory pattern and RVP responses to the induced SDH are shown in figure 59. In this group, the first parameter to respond was ICP, followed in sequence by MaBP, respiratory pattern, HR and RVP. The hemorrhage caused increases in ICP, MaBP, and RVP, bradycardia and other arrythmias, and respiratory pattern abnormalities.

In 2 of the 6 animals of the SDHRx group, the initial response of the MaBP was hypotension, with a mean decrease of 26±14 mm Hg. The hypotension progressed to hypertension within 12±4 seconds. Two of the 8 animals in the SAHRx developed hypotension, with a mean decrease of 13±5 mm Hg, lasting 10±5 seconds.

The initial response of the remaining 4 animals of the SDHRx group was hypertension. After the maximum MaBP response was reached, the MaBP returned to normal levels.

The mean times for "MaBP to change", "MaBP to peak" and "MaBP to recover" for the 2 groups are shown in tables 20,21. There were no significant differences in these times for the 2 groups, however the times to peak and to recover tended to be longer for the SAHRx group than these times for the SDHRx group. The peak MaBP values are presented in table 20, and they are not significantly different.

The initial response of HR to the insult was bradycardia occurring at 21±15 seconds after the start of the hemorrhage. The HR decreased to 82±12 beats/min. at 41±7 seconds following the initiation of the insult. The rate is similar to that of the SAHRx group, but it occurred sooner.

Three animals experienced HR less than 100 beats/minute. Of these, sinus bradycardia was present in 1 animal, junctional rhythm bradycardia in another, and the third animal had both sinus and junctional rhythm bradycardia. The remaining 3 animals developed slowing of HR, but not to less than 100 beats/minute. Other arrythmias present were PVB's, ventricular tachycardia, ventricular bigeminy, junctional tachycardia, and ventricular and junctional tachycardia with A-V block. There were T wave changes consisting of peaks and flattening in 4 animals. The EKG pattern returned to normal by CBF (5) in 5 of the 6 animals. In the other, the EKG recovered by CBF (7).

The EKG changes were similar to those of the SAHRx group.

Mean times for "ICP to change" and the "ICP to peak" for the 2 groups are shown in table 20. There is no significant difference between the corresponding times for the 2 groups.

The maximum ICP responses are shown in table 20. There is no significant difference between these, but that of the SAHRx group tended to be greater than that of the SDHRx group.

After the ICP peak, ICP fell rapidly at first, and then more slowly to a steady state level. The "half-time decay" and "time to recover" for the 2 groups are presented in table 21. There is no significant difference between these times of the 2 groups but those of the SAHRx group tended to be longer than those of the SDHRx group. At this recovery point, ICP of 4 of the 6 SDHRx animals was normal, and in the remaining 2 it was elevated to 24 mm Hg. In 1 of these ICP remained elevated for the duration of the studies, and in the other, it returned to normal at CBF (7).

The $\overline{\text{CPP}}$ and $\overline{\text{CPPl}}$ levels for the 2 groups are presented in table 21. There were no significant differences in these pressures of the 2 groups. Both the SDHRx and SAHRx exhibited similar initial responses of MaBP, HR, ICP and CPP to the insult.

MaBP, HR, ICP and CPP for both groups during the post-hemorrhage CBF determinations are presented in table 26. The pre and post- insult CPP levels are recorded graphically in figures 51 and 60.

For both groups at CBF (5), MaBP was significantly lower than resting, at $p<0.05$ for the SDHRx group, and at $p<0.01$ for the SAHRx group.

HR was significantly lower than resting in the SDHRx group ($p<0.05$), and for the SAHRx group it was less (ns) than normal.

The mean ICP of both groups returned to normal by this flow.

The CPP at CBF (5) for the SDHRx group was lower (ns) than normal, and that of the SAHRx group was significantly decreased ($p<0.01$).

At CBF (5), the SAHRx group demonstrated slightly greater (ns) decreases in MaBP and CPP; HR was more decreased (ns) in the SDHRx group. Treatment was instituted in both groups after CBF (5). The duration necessary to obtain adequate drug levels was not different between the 2 groups, and the CBF determinations during treatment were performed at similar times. Thus physiological parameter comparisons can be made at the same post-insult flow determinations for the 2 groups.

MaBP levels in the SDHRx group remained significantly lower than resting for CBF (6) ($p<0.01$) and CBF (7,8,9,10) ($p<0.05$) as did these levels in the SAHRx group (table 26). The relative MaBP decreases were slightly greater (ns) for the SAHRx group.

HR of the SDHRx group remained lower (ns) than resting at CBF (6) and above (ns) resting at CBF (7,8,9,10). In the SAHRx group, HR showed the same pattern, and the changes were not significant. The HR variations at corresponding flows for the 2 groups were not significantly different from each other.

ICP of the SDHRx group was normal for CBF (6,7) and elevated for CBF (8,9,10). Elevations in ICP were found in 3 animals at CBF (7) in 4 at CBF (8), in 5 at CBF (9) and in 4 at CBF (10). Mean ICP elevations at CBF (8,9,10) were not significant. The individual maximum ICP elevation was to 40 mm Hg. In the SAHRx group, ICP remained normal except for an elevation (n.s.) at CBF (8). At this flow, 2 animals demonstrated an ICP increase. The individual maximum was 32 mm Hg.

The CPP of the SDHRx group remained lower than resting at CBF (6,7,8,9,10) and the decrease was significant at CBF (6,9,10) (table 26). For the SAHRx group, CPP remained significantly lower than normal for the duration of the treatment studies (table 26). The respective CPP decreases experienced were not significantly different from each other.

On cessation of the treatment, MaBP at CBF (11) for the SDHRx group returned to within normal limits as did that at the SAHRx group. No significant differences were found between these 2 pressures.

HR for both groups was slightly greater (n.s.) than resting, and there were no significant differences between them.

ICP in the SDHRx group remained elevated (n.s.) above resting, and that of the SAHRx group was normal. At this flow, 4 animals in the SDHRx group had elevated ICP levels (maximum 34 mm Hg) and no animals in the SAHRx group had elevation of ICP.

The CPP level of the SDHRx group was lower (n.s.) than resting at CBF (11) and that at the SAHRx group was normal.

Both the SDHRx and SAHRx groups experienced MaBP and CPP decreases subsequent to the insult (CBF (5)). During treatment both groups demonstrated decreases in MaBP and CPP. On cessation of treatment, MaBP returned to normal in both, and CPP remained low for the SDHRx group and was normal for the SAHRx group. In general, ICP of the SDHRx group was elevated during the latter stages of treatment, and remained so after the discontinuation of the therapy. In the SAHRx group, ICP tended to remain normal during and after treatment.

The persistent decrease in CPP of the SDHRx group after treatment, despite normal MaBP, is explained on the basis of elevated ICP.

(b) Respiratory Pattern, Arterial Blood Gas, Alveolar-Arterial Oxygen Difference and Right Ventricular Pressure Changes.

Pre-insult Vt, RR, arterial blood gases, pH, A-aDO2 and RVP for the 2 groups are presented in table 27. There were no significant differences noted during the 4 pre-insult CBF determinations in the SDHRx group of Vt, RR, PaCO2, pH, A-aDO2 and RVP. For PaO2, the only significant difference noted was the PaO2 of CBF (3) being less than that of CBF (4) ($p<0.01$). The difference however was only 2 mm Hg. The overall means for the 4 flows are also shown in table 27.

The pre-insult physiological parameters for the SAHRx group have been presented in the previous section.

The initial respiratory pattern response to the insult in the SDHRx group, as was the case with the other groups, consisted of increases, decreases and no changes in Vt and RR. No specific pattern was demonstrated. These changes progressed in all animals to varying periods of apnea.

The mean times for the respiratory pattern to change in both groups are presented in table 20. No significant differences were present.

Mean lengths of apnea are shown in table 20. There were no significant differences, but the duration of apnea in the SAHRx group, tended to be longer than that of the SDHRx group.

The mean times for "respiration to recover" are also presented in table 21.

No significant differences were present, but this time for the SAHRx group tended to be slightly greater than the SDHRx group.

Arterial blood gases, pH and A-aDO2 were not documented during the insult.

The response of RVP to the hemorrhage for the SDHRx group, as with the SAHRx group, was hypertension. The RVP "time to change", "time to peak" and "time to recover" for both groups are shown in tables 20 and 21. No significant differences were found between these times of the 2 groups. However those of the SAHRx group tended to be longer than those of the SDHRx group. Maximum RVP responses are documented in table 20, and that of the SDHRx group is slightly greater (ns) than this value for the SAHRx group. In the SDHRx group, RVP responded after ICP, MaBP and respiratory pattern, peaked after ICP and MaBP, and was faster to recover than ICP and MaBP, but slower than the respiratory pattern. In the SAHRx group, RVP responses in relation to those of ICP, MaBP and respiration, followed the same patterns as those of the SDHRx group RVP. Both the SDHRx and SAHRx experienced similar initial responses of respiratory pattern and RVP to the insult.

The post-insult Vt, RR and arterial blood gases expressed as percentages of resting are shown in table 28. The actual post-hemorrhage values for pH, A-aDO2 and RVP are also presented in table 28. The actual measured PaCO2 and PaO2 for the 2 groups are shown graphically in figure 52, and A-aDO2 in figure 61.

At CBF (5), Vt of the SDHRx group was elevated (ns) above normal, and RR decreased (ns). The SAHRx group Vt and RR behaved similarly. These Vt increases were not significantly different from each other, and neither were the RR decreases, but the changes noted tended to be greater for the SDHRx group.

The $PaCO_2$ at CBF (5) for the SDHRx group was significantly lower than resting ($p<0.05$), as was that for the SAHRx group ($p<0.05$). These decreases were not significantly different from each other, but the SAHRx group tended to experience a greater decrease.

The SDHRx group experienced a significant decrease in PaO_2 at CBF (5) ($p<0.05$). PaO_2 at the SAHRx group was very minimally (ns) decreased, if a decrease was present at all. Change in PaO_2 for the SDHRx group was greater (ns) than that of the other group.

The pH of the SDHRx group was unchanged, and that of the SAHRx group was slightly elevated above (ns) resting.

Both the SDHRx and SAHRx groups experienced increases in $A\text{-}aDO_2$ at CBF (5), and that for the SDHRx group was significantly greater than resting ($p<0.05$). This increase for the SDHRx group was greater (ns) than that for the SAHRx group.

The RVP of both groups was slightly lower (ns) than resting. These decreases were not significantly different.

The Vt of the SDHRx group recovered to within normal limits by CBF (6), but remained slightly elevated (ns) for CBF (6,7,8) and significantly elevated at CBF (9,10) ($p<0.05$). For the SAHRx group, Vt was slightly elevated (ns) at CBF (6,9), slightly decreased (ns) at CBF (7) and normal at CBF (8,10). The corresponding Vt changes in the 2 groups were not significantly different from each other.

The RR of the SDHRx group was slightly elevated (ns) at CBF (6,7,9,10) and normal at CBF (8). For the SAHRx group, RR was normal for CBF (7,8,10) and slightly elevated (ns) at CBF (6,9). The RR variations of the 2 groups at corresponding flows were not significantly different from each other.

PaCO2 of the SDHRx group was lower than resting for the duration of the treatment studies, and significantly so at CBF (6,8,9,10) (table 28). Similarly, the SAHRx group experienced a persistently decreased PaCO2 during the duration of the treatment studies, which was significantly lower than resting at CBF (8,9,10) (table 28). The corresponding decreases in PaCO2 for the 2 groups were not significantly different from one another.

The PaO2 of the SDHRx group remained lower than resting at CBF (6,7,8,9,10) but only significantly so at CBF (9) ($p<0.01$), and at CBF (10) ($p<0.05$). The PaO2 of the SAHRx group remained slightly lower (ns) than normal for the duration of treatment studies. The corresponding PaO2 decreases for the 2 groups were significantly different at CBF (9,10) ($p<0.05$) with greater decreases in PaO2 occurring in the SDHRx group than the SAHRx group.

The pH of the SDHRx group was slightly elevated for the remainder of the treatment investigations. The increase was significant only at CBF (10) ($p<0.05$). In the SAHRx group, pH was normal at CBF (7) and slightly elevated (ns) for CBF (6,8,9,10). The corresponding increases in pH for the 2 groups were not significantly different from each other.

In the 2 groups, A-aDO2 remained elevated for CBF (6,7,8,9,10). This was significant for the SDHRx group at CBF (7,8) ($p<0.05$) and at CBF (9,10) ($p<0.01$). The elevations for the SDHRx group tended to be slightly greater (ns) than the corresponding elevations for the SAHRx group.

The RVP for the SDHRx group remained lower than resting for the duration of the treatment studies. The decrease was significant only at CBF (6) ($p<0.01$), and at CBF (7) ($p<0.05$). For the SAHRx group, RVP remained below normal, but only significantly at CBF (6,7) ($p<0.05$).

The corresponding RVP decreases for the 2 groups were significantly different from each other only at CBF (6) ($p<0.05$) with the PVP decrease of the SDHRx group being greater than that of the SAHRx group.

Following cessation of the treatment, CBF (11) was performed. At this flow, Vt and RR of both groups were increased. The only significant increase above resting, was Vt of the SDHRx group ($p<0.05$). The increase was only 3 ml. The relative Vt increases for the 2 groups were not significantly different from each other, and neither were the RR increases.

The PaCO2 of the SDHRx group was significantly lower than resting ($p<0.01$), as was that of the SAHRx group ($p<0.05$). These decreases were not significantly different from each other.

PaO2 of the SDHRx was less (ns) than resting and that of the SAHRx group was normal.

The pH of both groups was elevated (ns) above resting. No significant difference was present between these elevations.

A-aDO2 remained elevated at this flow in both groups, significantly so only for the SDHRx group ($p<0.01$). This elevation for the SDHRx group tended to be greater than that for the SAHRx group.

In both the SDHRx and SAHRx groups RVP was normal.

As has been noted in the SAHRx group, those animals in the SDHRx group experiencing a longer duration of RVP elevation following the insult showed a greater reduction in PaO2 and a larger elevation of A-aDO2.

The SDHRx and SAHRx groups exhibited similar responses to the insult of Vt, RR, arterial blood gas and pH, A-aDO2 and RVP immediately subsequent to the hemorrhage (CBF (5)) during the treatment regime, (CBF (6,7,8,9,10), and following cessation of the therapy (CBF (11)). However, the

SDHRx experienced more marked changes of Vt and PaO2 during the studies.

(c) Regional Cerebral Blood Flow and Cerebrovascular Resistance Responses.

The pre-insult rCBF and CVR for both groups are shown in table 25. There was no significant difference in the rCBF values during the pre-insult period of the SDHRx group. The only significant difference in the pre-SDH CVR was that of CBF (4) being greater than that of CBF (3) ($p<0.05$). The overall means for rCBF and CVR are also shown in table 25. The pre-SAH rCBF and CVR values for SAHRx group were discussed in the previous section.

The post-insult rCBF values for both groups are shown as a percentage of normal in table 26. The actual measured rCBF levels for the 2 groups are represented graphically in figures 51 and 60. Actual CVR values for both groups are shown in table 26 and graphically demonstrated in figure 62.

At CBF (5), following the insult, both groups experienced a highly significant decrease in rCBF ($p<0.01$). The SDHRx group rCBF was 25±3 ml/100gm/min and that of the SAHRx group was 20±2 ml/100 gm/min. The relative decreases of the 2 groups were not significantly different, but that of the SAHRx group tended to be greater. Both groups also showed a significant increase in CVR at CBF (5) ($p<0.01$). The relative increases were not significantly different from each other.

During the treatment program, CBF (6,7,8,9,10), rCBF of the SDHRx group remained significantly lower than resting ($p<0.01$). In the SAHRx group, rCBF also remained significantly below resting for this period ($p<0.01$). The corresponding CBF decreases for these 2 groups were not significantly different from each other, however, those of the SAHRx group tended to be greater.

In the SDHRx group CVR was slightly elevated (ns) above normal at CBF (6) and normal at CBF (7,8,9,10). The CVR for the SAHRx group remained above resting for CBF (6,7,8,9,10), but this was only statistically significant at CBF (10) ($p<0.05$). The increases in CVR in the SAHRx group were significantly greater than the CVR change for the SDHRx group at CBF (9,10) ($p<0.05$).

On cessation of the treatment, rCBF of the SDHRx group at CBF (11) remained unchanged from CBF (10), and remained significantly lower than resting ($p<0.01$). rCBF of the SAHRx group showed slight improvement at CBF (11) from CBF (10), but it was also significantly lower than control ($p<0.01$). The relative rCBF decrease from resting was not significantly different for the 2 groups, however that of the SAHRx tended to be greater than the decrease exhibited by the SDHRx group.

On cessation of the treatment, CVR of both groups increased. The CVR increase of the SDHRx group was not significantly different than resting, whereas that of the SAHRx group was (p<0.01). The relative CVR increase of the SAHRx group was significantly greater than that of the SDHRx group at CBF (11) (p<0.01).

Both groups responded similarly to the insult with rCBF decreases and CVR increases immediately following the insult (CBF (5)). The SAHRx group experienced greater change in these than did the SDHRx group. During the treatment regime, rCBF of both groups remained lower than resting, and CVR was increased during this period in the SAHRx group. The SDHRx group demonstrated a return to normal of CVR during the treatment. The SAHRx group again experienced greater changes in rCBF and CVR during the treatment program. On cessation of the regime, rCBF of both groups remained low and CVR was elevated. Greater changes in these parameters were again demonstrated in the SAHRx group compared to the SDHRx group.

(d) Cerebral Angiography

The mean pre-insult IDICA diameters for the 2 groups are shown in table 25. The post-insult caliber measurements expressed as a percentage of resting are presented in table 26. Actual IDICA measurements pre and post-injection for the 2 groups are shown graphically in figures 51 and 60. Representative cerebral angiograms for the 2 groups during the experimental studies are shown in figures

55(a),(b),(c),(d), and 63(a),(b),(c),(d).

The initial response to the hemorrhage in the SDHRx group was diffuse cerebral vasospasm, as was the case with the SAHRx group. Mean IDICA diameter of the SDHRx group was significantly smaller than resting ($p<0.01$). For the SAHRx group, the response was similar ($p<0.01$). The degree of narrowing was greater (ns) for the SAHRx group.

With treatment still in progress, cerebral angiography following CBF (10) for the SDHRx group demonstrates some recovery of the cerebrovasculature, but vasospasm was still present. In the SAHRx group, vasospasm was also prominent at this angiographic examination. Mean IDICA diameter of the SDHRx group improved, but still remained smaller (ns) than resting. For the SAHRx group, mean IDICA caliber remained significantly smaller than resting ($p<0.05$). The caliber recovery was less marked for this latter group.

Following cessation of the therapy, there was more recovery of the cerebrovasculature in the SDHRx group, but vasospasm was still present. This was similar to the occurrences in the SAHRx group. The SDHRx mean IDICA diameter measurement remained less (ns) than resting. Recovery of IDICA diameter in the SAHRx group was even less marked.

(e) Pulmonary Pathology

Gross examination revealed the lungs of the animals in this group to be normal. The mean weight of the lungs was 22.3± 1.9 gm.

Histologically, 1 animal had completely normal lungs; 2 animals had very mild to moderate intra-alveolar and interstitial edema; 1 animal had marked intra-alveolar edema with hemorrage and mild interstitial edema; and in the final animal, 1 lung was normal and the other had very mild intra-alveolar edema. The lungs displaying moderate to marked intra-alveolar edema and/or interstitial edema were heavier (26±1.0 gm) than the overall mean. Figure 64 shows the appearance of moderate interstitial edema seen in this group.

(iii) The Effects Of Simultaneous Intravenous Infusions Of Sodium Nitroprusside And Phenylephrine In The Spontaneously Breathing Primate.

(a) Cardiovascular and Intracranial Pressure Responses.

This section deals with the effects of the treatment regime in 3 animals that do not receive an insult. The results of the SAHRx and SDHRx groups will also be presented here for contrasts and comparisons.

The mean weight of the experimental animals in this group is shown in table 1 and is not significantly different from those of the other groups.

Means, and SEM for MaBP, HR, ICP, and CPP for CBF (1,2,3,4) for the 3 groups are presented in table 29. Within the treatment alone group, (Rx alone), there were no significant differences over the 4 flows for either MaBP or CPP. For HR, the only significant difference was the HR for CBF (4) being greater than that at CBF (1) ($p<0.01$). The overall means are also presented in table 29. ICP was first measured at CBF (4). These physiological parameters for the SAHRx and SDHRx group have been discussed in the 2 previous sections.

The Rx alone group did not receive an intracranial insult. After an appropriate amount of time had elapsed, corresponding to the time necessary to perform the insult in the other groups, CBF (5) was initiated. During this time period, there were no changes in MaBP, HR or EKG, ICP or CPP, apart from normal physiological variations.

At CBF (5), MaBP of the Rx alone group was within normal limits, whereas the MaBP values of the SAHRx and SDHPx groups were significantly less than resting ($p<0.01$ and $p<0.05$ respectively).

HR for the Rx alone group at this flow was unchanged. For the SAHRx group, HR was slightly less (ns) than normal, and for the SDHRx group it was significantly lower than resting ($p<0.05$).

ICP for all 3 groups was normal at CBF (5).

CPP for the Rx alone group was normal; it was significantly decreased in the SAHRx group ($p<0.01$) and less thanb normal (ns) in the SDHRx group.

MaBP, HR, ICP and CPP for the remainder of the studies for the 3 groups are shown in table 30. The CPP levels for each group are also shown graphically in figures 51,60 and 65.

During CBF (5), the physiological parameters measured remained normal for the Rx alone group, whereas decreases in MaBP, HR and CPP were present in the SAHRx and SDHRx groups as previously described.

With the initiation of treatment prior to CBF (6), MaBP of the Rx alone group fell. It remained lower (ns) than normal for the duration of the treatment studies, CBF (6,7,8,9,10). MaBP of both the SAHRx and SDHRx studies reamined significantly lower than normal for the duration of the treatment studies. The MaBP decreases present in the Rx alone group were not significantly different from the corresponding decreases at the SAHRx and the SDHRx groups. The relative decreases of the Rx alone group tended to be less than those of the SAHRx group and similar to those of the SDHRx group.

HR of the Rx alone tended to be slightly increased, and at CBF (8) it was significantly greater than normal ($p<0.01$). For the other treatment groups, HR was decreased (ns) at CBF (6) and elevated (ns) at CBF (7,8,9,10). The relative changes in HR during the treatment regime for the 3 groups were not significantly different from one another.

ICP of the Rx alone group tended to show elevations (ns) above resting during the treatment program. During this time, 1 animal showed a persistently elevated ICP, and another fluctuated between normal and elevated. The maximum ICP was 28 mm Hg. The ICP of the remaining animal was normal throughout. In the SAHRx group, ICP was normal except for an elevation (ns) during CBF (8) in 2 animals. For the SDHRx group, some of the experimental animals demonstrated elevated ICP (ns) during CBF (7,8,9,10) as described in the previous section.

CPP of the Rx alone group was less than normal for the duration of the treatment studies. These decreases were significantly lower than normal at CBF (7,10) ($p<0.05$). CPP of the SAHRx group at CBF (6,7,8,9,10) was significantly lower than resting (table 30). In the SDHRx, CPP was lower than normal for the remainder of the treatment investigations, and significantly so at CBF (6,9,10) (table 30). The corresponding CPP decreases for the 3 groups were not significantly different from one another.

After discontinuation of the treatment program, CBF (11) was performed. At this flow, MaBP of the Rx alone group showed an increase, but remained slightly less (ns) than control. Similarly the MaBP of the other treatment groups returned to within normal levels. The small differences present between CBF (11) MaBP and normal for the 3 groups were not significantly different from one another.

All 3 groups showed slight HR elevations (ns) above normal at this flow. The relative increases of these groups were not significantly different from one another.

Mean ICP of the Rx alone group was slightly elevated (ns) at CBF (11). Increased ICP was present in only 1 animal (25 mmHg). In the SAHRx group, the ICP was normal. For the SDHRx group, ICP was slightly elevated (ns). ICP elevations were present in 4 experimental animals. The relative ICP increases for the Rx alone and SDHRx groups were not significantly different from each other.

In the Rx alone group, the CPP remained lower (ns) than normal at CBF (11). CPP of the SAHRx group was normal, and for the SDHRx group, it was lower (ns) than resting. No significant difference was present between the relative CPP reduction of the Rx alone group compared to that of the SDHRx group. The CPP of the Rx alone group remained less than normal because of a slightly decreased mean MaBP and slightly elevated mean ICP.

During the treatment program, all 3 groups showed decreases in MaBP and in CPP, that were not significantly different from one another at corresponding CBF determinations for these groups. In general, HR increases were present during the treatment for all groups, and again, these elevations were not significantly different from one another. ICP in the Rx alone and SDHRx groups tended to be elevated, and that of the SAHRx group was normal.

On cessation of the treatment the MaBP levels of the 3 groups recovered towards normal as did the CPP. Both these values tended to be slightly decreased (ns) in the Rx alone group. HR was slightly elevated for all 3 groups. Mean ICP was minimally increased in the Rx alone group (elevated in 1 animal and normal in 2) and was elevated (ns) in the SDHRx group. In the SAHRx group ICP was normal at CBF (11).

(b) Respiratory Pattern, Arterial Blood Gas, Alveolar-Arterial Oxygen Difference and Right Ventricular Pressure

Changes.

The respiratory pattern parameters (Vt,RR), arterial blood gases, pH, A-aDO2 and RVP for CBF (1,2,3,4) for all 3 groups are shown in table 31. No significant differences were found in these parametric measurements in the Rx alone group during the first 4 CBF determinations.

These physiological parameters of the SAHRx and SDHRx groups have been discussed in the previous 2 sections.

For the 3 groups, Vt, RR, PaCO2 and PaO2, of the remaining CBF studies, expressed as a percentage of normal are shown in table 32. The pH, A-aDO2 and RVP are presented as actual values in table 32. The actual measured PaCO2 and PaO2 values for all 3 groups are presented graphically in figure 52, and A-aDO2 in figure 66.

At CBF (5), mean Vt of the Rx alone group was minimally elevated (ns) above normal, and RR was normal. In the SAHRx and SDHRx groups, mean Vt showed larger increases above resting, but they were not significantly greater than normal. These 2 groups also showed RR decreases (ns) from resting. The relative increases in Vt of the 3 groups were not significantly different from one another, nor were the RR decreases.

PaCO2 of the Rx alone group was normal at CBF (5), and the PaCO2 values at the SAHRx group and the SDHRx group were significantly lower than resting ($p<0.05$).

PaO2 of both the Rx alone and SAHRx groups was normal, and that at the SDHRx was reduced (ns) from normal.

pH of the Rx alone group and SDHRx group at CBF (5) were normal, and that of the SAHRx group was increased (ns).

A-aDO2 of the Rx alone group showed minimal elevation (ns) above resting. These values for the other 2 groups showed greater elevations than the Rx alone group, significantly so for the SDHRx group ($p<0.05$).

RVP of the Rx alone group was normal at CBF (5) and was reduced (ns) in the SAHRx and SDHRx groups.

At CBF (5) the SAHRx and SDHRx groups tended to show greater changes in Vt, RR, PaCO2, PaO2, pH, A-aDO2, and RVP than did the Rx alone group.

During the treatment program, Vt of the Rx alone group was normal at CBF (6,7) and elevated (ns) at CBF (8,9,10). For the SAHRx group, Vt was slightly elevated (ns) at CBF (6,9) slightly decreased at CBF (7) and normal at CBF (8,10). In the SDHRx group, Vt was normal at CBF (6) and elevated for the remainder of the treatment studies (table 32). The corresponding Vt changes for the 3 groups were not significantly different from each other.

RR for the Rx alone group was slightly elevated (ns) at CBF (6,9,10) and slightly decreased (ns) at CBF (7,8). For the SAHRx group, RR was normal at CBF (7,8,10) and slightly elevated (ns) at CBF (6,9). In the SDHRx group, RR was normal at CBF (8) and slightly elevated (ns) at CBF (6,7,9,10). The corresponding RR changes in these 3 groups were not significantly different from one another.

PaCO2 remained slightly less (ns) than resting in the Rx alone group, as did the PaCO2 values of the other 2 treated groups. The decreases in the SAHRx group at CBF (9,10) tended to be greater than the Rx alone group. The corresponding PaCO2 changes during CBF (6,7,8,9,10) for the 3 groups were not significantly different from one another.

PaO2 during the treatment program for the Rx alone group was normal at CBF (8) and slightly decreased (ns) at CBF (6,7,9,10). The PaO2 of the SAHRx group remained slightly lower (ns) than resting for the duration of the treatment studies. In the SDHRx group, PaO2 was lower than resting for the remainder of the treatment program, and it was significantly decreased at CBF (9,10) ($p<0.01, p<0.05$ respectively). There were no significant differences in the corresponding PaO2 decreases of the 3 groups, but those of the SAHRx and SDHRx groups tended to be greater than those of the Rx alone group.

The Rx alone group had normal pH at CBF (6,7,8) and slightly elevated (ns) pH at CBF (9,10). For the SAHRx group, pH was normal at CBF (7) and slightly elevated (ns) at CBF (6,8,9,10). In the SDHRx group, pH was normal at CBF (6) and elevated at CBF (7,8,9,10). The pH elevation was significantly greater than resting only at CBF (10) ($p<0.05$). The corresponding increases in pH for the 3 groups were not significantly different from one another.

A-aDO2 was elevated for the duration of the treatment studies in all 3 groups, and the increases of the SAHRx and SDHRx groups tended to be greater that that at the Rx alone group. This was only significant for the SDHRx group at CBF (9) ($p<0.05$).

RVP in the Rx alone group was slightly lower (ns) than normal during the treatment program. For the SAHRx group, RVP was below resting, and significantly so at CBF (6,7) ($p<0.05$). In the SDHRx group, RVP was also lower than resting, but significantly so at CBF (6) ($p<0.01$) and at CBF (7) ($p<0.05$). The corresponding decreases in RVP experienced by the 3 groups were not significantly different from each other.

At CBF (11), following discontinuation of the treatment program, Vt of the Rx alone was elevated (ns) above the accepted normal and RR was normal. For the SAHRx group both Vt and RR were increased (ns) above resting. The same occurred in the SDHRx group, and the Vt increase was significant ($p<0.05$). The corresponding changes in Vt were not significantly different between the 3 groups, nor were those of RR.

The PaCO2 of the Rx alone group was slightly decreased (ns). Both the SAHRx and SDHRx groups demonstrated a significant decrease in PaCO2 at CBF (11) ($p<0.05$, $p<0.01$). The corresponding decreases of the 3 groups were not significantly different from each other.

PaO2 at the Rx alone group was lower (ns) than normal, as was that of the SDHRx group. The corresponding decreases were not significantly different from each other. PaO2 of the SAHRx alone group was normal.

pH of the Rx alone group was normal, and that of the other 2 groups was elevated (ns) above resting.

A-aDO2 remained elevated for the 3 groups at this flow (table 32). For the Rx alone group, A-aDO2 was significantly greater than resting ($p<0.05$). No significant differences were present between the elevations at this flow.

RVP of all 3 groups were normal at this CBF determination.

In general, the respiratory pattern, PaCO2, pH and RVP of the 3 groups behaved similarly during and after the treatment program. The PaO2 decreases present during the treatment regime tended to be greater for the SAHRx and SDHRx groups than those of the Rx alone group. At CBF (11), after the treatment, PaO2 was low for both the Rx alone and SDHRx groups, and normal for the SAHRx group.

A-aDO2 tended to remain elevated during the treatment program for all 3 groups, but more so for the SAHRx and SDHRx groups. Similarly, after treatment cessation, A-aDO2 for the 3 groups was elevated.

(c) Regional Cerebral Blood Flow and Cerebrovascular Resistance Changes.

rCBF and CVR for all 3 groups during CBF (1,2,3,4) are presented in table 29. No significant differences were present in either rCBF or CVR for the Rx alone group determined over the first 4 CBF determinations. These physiological parameters for the SAHRx and SDHRx groups are discussed in the previous 2 sections. The overall means are also presented in table 29.

rCBF expressed as a percentage of normal for the groups for CBF (5,6,7,8,9,10,11) are presented in table 30. The actual CVR levels for this period are also shown in table 30. The actual measurements of rCBF for the groups are presented graphically in figures 51,60 and 65, and those for CVR in figure 67.

At CBF (5), rCBF of the Rx alone group was within normal limits, or just minimally decreased and for the SAHRx and SDHRx groups, rCBF was significantly lower than resting ($p<0.01$). The decreases in rCBF of these 2 groups were significantly greater than the changes in rCBF at CBF (5) for the Rx alone group ($p<0.01$).

CVR of the Rx alone group demonstrated a significant increase compared to the first 4 flow values ($p<0.01$) at CBF (5). The increase, however, was small, in the neighborhood of 0.23 units, representing an increase of 14%, and resulted from a minimal decrease in rCBF in 2 of 3 animals at this flow. Both the SAHRx and SDHRx groups experienced a significant increase in CVR at this flow ($p<0.01$). These increases were both 1.27 units above resting, representing elevations of 79% in the SAHRx group and 77% in the SDHRx group, and were both significantly greater than the increase in the Rx alone group ($p<0.01, p<0.05$).

At CBF (5), the SAHRx and SDHRx groups experienced significantly greater decreases in rCBF and significantly larger increases in CVR than did the Rx alone group.

During the treatment period, CBF (6,7,8,9,10), rCBF of the Rx alone group was slightly lower (ns) than normal, whereas rCBF of the SAHRx and SDHRx group remained significantly lower than resting ($p<0.01$). The corresponding reductions in rCBF of the 3 groups were not significantly different from one another, except for the reduction of the SAHRx group being greater than that of the Rx alone group at CBF (9) ($p<0.05$). In general however, the reductions present in the SAHRx and SDHRx groups tended to be greater than those of the Rx alone group.

CVR for the Rx alone group was slightly lower (ns) than resting during this period (CBF (6,7,8,9,10). In the SAHRx group, CVR remained above resting but only significantly at CBF (10) ($p<0.05$). For the SDHRx group, CVR was slightly elevated (ns) at CBF (6), and normal at CBF (7,8,9,10). The changes experienced by the Rx alone and SDHRx groups at corresponding flows were not significantly different from one another. For the Rx alone and SAHRx groups, corresponding CVR changes were not significantly different, except at CBF (9,10) with CVR of the SAHRx group being significantly reduced compared to the changes in CVR of the Rx alone group ($p<0.05$).

After treatment cessation, CBF (11) was performed. rCBF for the Rx alone group was significantly lower than normal ($p<0.05$). For the SAHRx and SDHRx groups, rCBF at CBF (11) was significantly reduced ($p<0.01$). The corresponding reductions were not significantly different from one another, however, that of the SAHRx and SDHRx groups tended to be greater than the rCBF reduction of the Rx alone group.

CVR at CBF (11) of the Rx alone group was slightly increased (ns) above normal. The increase was only 0.17 units, representing a 10% increase. In the SAHRx group, CVR was significantly elevated above resting ($p<0.01$). The increase was 1.59 units, a 100% increase above resting. For the SDHRx groups, CVR was elevated (ns) above normal. The increase was 0.38 units representing a 23% increase above resting. The CVR increase of the SAHRx group was significantly greater than that of the Rx alone group

$(p<0.05)$, and that of the SDHRx group only tended to be larger than the CVR increase of the Rx alone group.

During the treatment program, the SAHRx and SDHRx groups experienced greater decreases in rCBF than did the Rx alone group. CVR during this period for the SAHRx group remained elevated; normal (except increase at CBF (6)) for the SDHRx group, and slightly decreased in the Rx alone group.

Following the discontinuation of the therapy, rCBF of the SAHRx and SDHRx groups tended to be lower than that of the Rx alone group. CVR elevations of the 2 hemorrhage groups were greater than the CVR increase in the Rx alone group.

(d) Cerebral Angiography

Mean IDICA diameters at the first set of cerebral angiograms for the 3 groups are shown in table 29. The vessel caliber measurements as percentages of normal, of the remaining angiographic examinations are presented for all the groups in table 30. Actual diameter measurements are shown graphically in figures 51,60 and 65. Cerebral angiograms representative of these 3 groups during the experimental investigations are presented in figures 55(a)-(d), 63(a)-(d) and 68(a)-(d).

The cerebrovascular status of the Rx alone group remained unchanged during the studies, compared to the cerebral vasospasm experienced by the other 2 treatment groups. The mean IDICA diameter of the second, third and fourth sets of cerebral angiograms remained unchanged from resting in the Rx alone group, as compared to the reduction in caliber previously described for the SAHRx and SDHRx groups.

(e) Neurological Examination

Neurological assessment of all animals in the SAHRx, SDHRx and Rx alone groups was carried out at the 5 hour and 20 hour observation periods using the 5 point grading system previously described. Table 33 shows the neurological assessments for these groups, as well as those of the 1.67 ml/kg SAH and artificial CSF groups for comparisions.

In the SAHRx group, 2 animals died acutely prior to the 5 hour examination. The remaining 6 animals were obtunded. All animals in this group were dead at 20 hours post-SAH. The poor neurological status of the animals in this group at both assessments, is similar to that occurring in the 1.67 ml/kg SAH group.

In general, the SDHRx group animals were somnolent and lethargic at the 5 hour neurological examination. At the 20 hour assessment, 5 animals were neurologically normal and 1 was dead. These results resemble those of the 1.67 ml/kg SDH group.

For the Rx alone group, the experimental animals at the 5 hour assessment were generally lethargic. All 3 animals died before the 20 hour final examination. One animal, observed until it's demise, developed severe metabolic acidosis with hyperventilation and a normal PaO2, and subsequently died.

As with the volume studies, the animals perfused with gurtaraldehyde were sacrificed via this method during their downhill course form which I felt there was no recovery. These animals were considered grade 5.

(f) Pathological Examination of Brain

As with the SAH volume, SDH and artificial CSF groups, the dura was examined after removal of the ICP device. The grading scale was the same as previously described.

In the SAHRx group, examination by palpation, revealed the dura in general to range from full to tight.

The dura of the animals in the SDHRx group included normal, slightly full and tight.

In the Rx alone group of animals, the dura examination ranged from normal to full.

Postmortem brain examination in the SAHRx group, using the previously described grading system, showed the brains to be swollen, and in 1 it was bulging, when the dura was incised.

In the SDHRx group, the brains appeared normal. Two of the brains in the Rx alone group appeared normal, and the other was slightly swollen.

Mean fresh brain weights for the 3 treatment groups, the 1.67 ml/kg SAH group and the artificial CSF group are shown in table 34. The numbers in parenthesis document the number of animals in the calculation. The remaining animals were either perfused with glutaraldehyde, or their brains were not weighed.

Intraventricular hemorrhage was present in 3 of the 8 animals in the SAHRx group. Only 1 animal in this group had ventricular dilatation, and it also had intraventricular blood.

In both the SDHRx and Rx alone groups, no intraventricular blood or ventricular dilatation was present.

Of the 3 acutely dying animals in the SAHRx group, 2 had intraventricular blood, and none had ventricular dilatation.

(g) Electron Microscopy

In the treatment investigation, 2 animals were perfused with glutaraldehyde for E.M. study of the cerebral vessels.

One animal was from the SAHRx group, and the other from the Rx alone group. The vessels studies were IDICA, MCA, PPA and DPA. The grading of intimal changes was a 4 point system as previously described for the first major investigation and the results for this study are shown in table 35.

In the SAHRx group, there was marked intimal infolding and undulation (grades 2-3). The IDICA was not studied. Cerebral angiograms of this animal in the pre-SAH state and immediately prior to glutaraldehyde perfusion are shown in figures 69(a),(b). Marked diffuse cerebral vasospasm is present in the latter angiogram. The cerebral vessel sites studied by E.M. are shown on this angiogram. Figures 70(a),(b) demonstrate the severe undulation and intimal infolding present in the cerebral vessels of this animal. Intimal muscle contraction is also present (fig. 70(c)). The media musculature is markedly contracted; the muscle cells are shortened, the borders are serrated, and the nuclei are folded and bulky. Figure 71 demonstrates a contracted media muscle cell with a kinked nucleus.

The cerebral vessel appearance in this group is similar to that of the 1.67 ml/kg SAH group shown in the previous section.

In the Rx alone group, the animal studied was in respiratory difficulty demonstrating tachypnea, and marked metabolic acidosis (pH=7.11) before glutaraldehyde perfusion. Cerebral angiograms performed prior to the perfusion showed evidence of mild diffuse spasm (fig. 72(a),(b)). The E.M. studies revealed minimal intimal undulation (grade 1) in association with mild contraction of the media musculature (fig. 73(a),(b)). These changes from a normal presentation are considered to represent minimal spasm.

(h) Pulmonary Pathology

Of the 3 animals in this group, 1 was perfused with glutaraldehyde. The mean weight of the lungs of the other 2 animals was 17.9± 1 gm. Gross appearance of the lungs was normal. Miscroscopic examination revealed the lungs of 2 animals (including the 1 perfused with glutaraldehyde) to be completely normal. The lungs of the third animal were normal with some areas of very mild interstitial edema. Figure 74 shows the appearance of normal pulmonary tissue exemplified by the experimental animals in this group.

CHAPTER IV

DISCUSSION

PREAMBLE

As was noted in the Introduction to this thesis: "Acute death or severely compromised neurological status continue to be the outcomes of subarachnoid hemorrhage in approximately 50% of patients suffering ruptured intracranial aneurysms. The mechanisms responsible for this high morbidity and mortality remain elusive".

The initial major investigation reported upon here has attempted to define and elucidate the processes contributing to the poor quality of survival following subarachnoid hemorrhage. In a spontaneously breathing primate model the pathophysiological responses to induced SAH (prechiasmatic cistern) were studied using 4 different volumes of fresh autogeneous blood. Twenty experimental animals were utilized for this particular investigation (5 in each volume group) the objectives of which were twofold:

(i) to study the pathophysiological responses at different SAH volumes and to document differences in response which are related to increasing SAH volume; and

(ii) to define a so-called "LD50" volume for our experimental model (i.e. the volume at which survival at 5 hours was 50%), a volume that would be employed in subsequent investigations of treatment efficacity.

The acute survival (5 hours) for both the 1.67 and 2.0 ml/kg SAH groups was 60%, and we believed the "LD50" volume to be within this range. Using 1.67 ml/kg body weight we subsequently studied the responses to subarachnoid injection of artificial CSF in 5 experimental animals.

The final study of the first major investigation was a subdural hemorrhage series using 4 animals; 2 receiving 1.67 ml/kg body weight and 2 2.0 ml/kg. The small number of experimental animals in this particular series does not allow us to make a definite statement concerning the pathophysiological responses to subdural blood in our experimental model.

These initial studies were primarily concerned with defining the insult-responses that were due to ICP changes; to the mode of increasing ICP; to the fluid medium (blood or artificial CSF) in the subarachnoid space; and to the various combinations of these parameters studied.

The second major investigation carried out concerned the treatment of reduced CBF and increased CVR following induced SAH and SDH. Three separate substudies were performed:

(i) a SAH series consisting of 8 experimental animals receiving an insult of 1.67 ml/kg body weight followed by treatment.

(ii) a SDH series of 6 animals receiving 1.67 ml/kg body weight followed by treatment.

(iii) a group of 3 animals receiving treatment without an intracranial insult.

These investigations concerned the effects of the treatment regime on otherwise normal experimental animals and its effectiveness in improving post-insult CVR increase, CBF decrease and survival.

Throughout both major investigations the cardiovascular parameters documented were MaBP, HR and EKG. Respiratory and pulmonary status were monitored by Vt, RR, arterial blood gases, pH and A-aDO2. In addition RVP was determined in the artificial CSF group and in the 3 substudies of the treatment investigations. ICP was measured throughout the studies, and CPP was calculated as MaBP-ICP. Regional CBF was determined using the radioisotope (133 Xenon) clearance technique described by Lassen et al (233).

Cerebral angiography documented the status of the larger conductance vessels both pre and post-insult, and CVR (calculated as CPP/CBF) was used to assess the state of the complete cerebrovascular tree including the smaller resistance vessels.

Gross postmortem examination was performed on all brains, and microscopic examination carried out for 3 animals in the SAH volume studies. Electron microscopic evaluation of the cerebral vessels (IDICA, MCA, CA, DPA, VA and BA) was carried out in 20 animals perfused with glutaraldehyde (SAH volume series: 8,SDH volume series: 2, artificial CSF series:4, SAHRx series: 1, SDHRx series: 0, Rx alone series: 1. The remaining 4 animals studied were those that received intracerebral hemorrhages.).

In the artificial CSF group, as well as in the treatment studies, the lungs were examined both grossly and by light microscopy.

In general, the measured physiological parameters remained unchanged during the 4 pre-insult CBF determinations in all groups, demonstrating stability of the experimental preparations during this period.

The initial part of this discussion will deal with the pathophysiological responses during and immediately following the various insults.

INTRACRANIAL PRESSURE AND CARDIORESPIRATORY RESPONSES

In our experimental studies, peak ICP was attained at the completion of the intracranial injection. Following this time, the ICP level fell spontaneously towards resting levels. This type of response is similar to "type 1" ICP pattern described by Nornes (110) in patients following SAH due to aneurysmal rupture. In Nornes' study (246), the ICP gradually increased after the initial fall indicating cerebral ischemia and edema. We did not observe this secondary increase in our studies except in the treatment series. We concluded, however, that the secondary ICP increase was due, not to edema, but to the cerebrovascular responses to the treatment regime.

In general, the ICP in all groups studied returned (at least initially) to normal resting levels soon after the insult. There were, however, several experimental animals in the larger SAH groups that had persistently elevated ICP following the hemorrhage. Recovery of ICP to a steady state near to or within normal pre-insult range following SAH has been observed by Steiner et al (216) with repeated SAH in dogs. Other investigators have found similar ICP recovery patterns following: SAH; subdural and subarachnoid (convexity, chiasmatic cistern, cisterna magna and lumbar) injections of saline and artificial CSF; intraventricular infusions, and subdural balloon inflation (217,218,247, 248,249). The ICP usually returns to resting levels if the insult volume is not too large, and if the ICP elevation is not deliberately maintained (114,216,247,248). The recovery results from the spatial compensatory mechanisms within the cranium. The main intracranial contents are brain, blood and CSF. Maintenance of a steady ICP in the face of increasing intracranial volume results from spatial reorganization of these components. The initial main buffering mechanism has been suggested to be the outflow of CSF along the craniospinal axis (250,251). There is also CSF displacement into the subarachnoid sheaths surrounding the cranial nerves (252,253) and possibly the spinal nerves (252). Most likely, the normal absorptive actions of the arachnoid granulations are also involved (252). On exhaustion of these mechanisms, cerebral blood volume and cerebral tissue become compromised, and ICP rises and remains elevated (248).

Steiner et al (114) demonstrated in dogs that repeated subarachnoid injections of whole blood, as well as red blood cells alone, were more effective in maintaining elevated ICP than similar injections of plasma and saline. They postulated that these differences resulted from an increase in CSF outflow resistance by red blood cells blocking CSF absorption over the convexity. Similarly, McQueen and Jelsma (112) have reported a subarachnoid block to free flowing CSF following induced SAH in dogs. Other investigators have also demonstrated subarachnoid blocks following SAH, however, the site of the block has not as yet been determined (252,254). Bradford et al (252) found a marked degree of blockage to the free passage of subarachnoid saline post-SAH, and suggested that perhaps all CSF outflow routes were affected. Obstruction at the tentorium and foramen magnum, either by cerebral tissue herniation (250) or by clotted blood, may disturb the normal outflow CSF pathways following SAH.

With a subarachnoid block the CSF outflow resistance increases and the normal spatial compensatory mechanics are disrupted. This then results in greater ICP changes and longer durations of ICP elevation following increases in intracranial volume.

Our results demonstrate that subsequent to subarachnoid injection of artificial CSF, ICP peaked at the completion of the injection and then rapidly fell to normal levels. With the SAH groups, ICP tended to remain elevated for longer periods of time in the larger SAH volume groups than in the smaller SAH volume groups. Following the insult in the SDH groups ICP was elevated for a longer duration than that in the artificial CSF group, but shorter than this time period in the smaller volume SAH groups. Spatial compensation following SDH was most likely by CSF outflow mechanisms as well as blood distribution throughout the potential subdural space.

Postmortem examination of the brains of those animals subjected to SAH revealed the diffuse presence of blood and blood clot over the convexities as well as throughout the basal cisterns. Larger amounts of blood were observed in the subarachnoid space of animals in the larger volume groups. This finding may explain the longer duration of ICP elevation in the large volume SAH animals and also the differences in ICP changes exhibited by the SAH group as compared with the SDH and artificial CSF groups resulting from blockage of CSF outflow.

Subsequent to the insult and in association with elevated ICP, hypertension, cardiac arrythmias (especially bradycardia) and various respiratory pattern disturbances leading to apnea of varying duration was observed in all experimental groups. The concomitant association of increased ICP, arterial hypertension, bradycardia and respiratory irregularities is generally known as the Cushing phenomenon (255) or the "Cushing triad" (248). Astley Cooper, in 1824 (256) demonstrated the development of bradycardia and diminished level of consciousness with crude finger pressure on the exposed surface of the brain of experimental animals. von Bergman, in 1880 (257), showed in laboratory animals that bradycardia and slow respirations accompanied increased ICP, and when ICP equalled the systolic blood pressure death ensued. Similarly, Naunyn and Schreiber, 1881 (258) demonstrated arterial hypertension following ICP elevation above mean arterial blood pressure. In both monkeys and dogs, Cushing (38,259) documented that when ICP approximated or was greater than the systolic blood pressure, arterial hypertension, bradycardia and various types of respiratory abnormalities, ranging from deep, stertorous respirations to respiratory slowing and apnea occurred. He described these changes as resulting from anemia to the medullary centres due to elevated ICP and pressure on the medulla. He later supported his experimental evidence with clinical data (222), and postulated that, subsequent to medullary anemia the vasomotor centre was stimulated resulting in peripheral and splanchnic vasoconstriction, which in turn gave rise to arterial hypertension. Vagus centre stimulation resulted in bradycardia, and respiratory centre anemia was responsible for the respiratory pattern changes. Cushing believed that the occurrence of arterial hypertension was a response to maintain medullary perfusion under conditions of elevated ICP.

Since these early observations, there has been much controversy over whether these phenomena really do occur, and at what level of ICP elevation they are observed. In experimental studies with patients, Browder and Meyers (260) were unable to elicit these responses until ICP surpassed either the diastolic or mean arterial blood pressure. They did report however, that when changes in blood pressure, heart rate and respiratory pattern did occur, these were quite variable and not necessarily in accord with the classic pattern described by Cushing (38). Similarly, Fremont-Smith et al (261) in patients with various intracranial disorders, did not find a hypertensive response until ICP exceeded that of the diastolic blood pressure. Evans et al (255) were not able to elicit the Cushing phenomenon in patients with rapid artificial elevation of ICP to mean MaBP levels by intraventricular infusion of saline, whereas they were repeatedly able to elicit these responses in rhesus monkeys following subdural oil injection resulting in ICP approaching the arterial blood pressure. Other investigators in the experimental field have demonstrated the vasopressor response with ICP elevation not exceeding MaBP (217,219,247,248,262,263). The association of elevated ICP and arterial hypertension has frequently been observed in the clinical sphere. Gobiet et al (264) have reported this occurrence in patients suffering head injuries.

The development of arterial hypertension with increased ICP in some studies and not in others has been felt by some investigators to be due to the rate at which ICP is elevated. Using rhesus monkeys Weinstein et al (247) were unable to show any differences in the vasopressor response following slow or rapid ICP elevation. Similarly, Zidan et al (265), in cats found the development of the Cushing response to be independent of the rate of expansion of a supratentorial balloon, but to be dependent upon a "critical volume". On the other hand, Nakatani et al (263) and Pathak et al (219) demonstrated greater vasopressor changes with rapid as compared with slow ICP increases.

The conflicting results concerning the occurrence of arterial hypertension, and its development following elevated ICP in both experimental and clinical investigations may be due to differences in experimental design:

(1) the various methods used to increase ICP may yield different results viz., a uniform elevation of supratentorial ICP via subarachnoid injection will most

likely cause different effects than epidural balloon inflation, with possible cerebral compression and distortion. Similarly cisterna magna injections may yield different results than basal cistern or convexity subarachnoid infusions.

(2) different techniques of monitoring ICP may also lead to the discrepancies reported in the literature. Cisterna magna and spinal fluid pressure determinations do not always reflect the true supratentorial pressure as accurately as do intraventricular and convexity measurements. This results from CSF fluid dynamics and intracranial pressure-volume relationships. Some of the conflicting results may be explained on the basis of the various techniques of ICP elevation and measurement used in the studies.

In general, the association of arterial hypertension following increased ICP is widely accepted. However, the processes by which the arterial blood pressure becomes elevated also remain controversial. As was previously noted, Cushing (38,259) described arterial hypertension to result from splanchnic and peripheral vasoconstriction. Brown (266) supports this theory, and has demonstrated the pressor response to be associated with increased peripheral vascular resistance which she believed to result from sympathetic stimulation. Rodbard et al (267,268) postulated that increased peripheral vascular resistance was due to the release of epinephrine-like neurohumoral agents into the circulation following elevated ICP. Peerless and Griffiths (269) and Benedict et al (270) have reported increases in plasma catecholamine levels following SAH in patients thus adding plausibility to the neurohumoral theory of peripheral vasoconstriction. Similarly, Graf and Rossi (271,272) have found increased blood and plasma catecholamine levels in dogs with artificially elevated ICP.

Freeman et al (273) believe that the vasopressor response is of cardiac origin. They theorized that neural and humoral sympathetic effects on the heart cause increases in cardiac output with resultant arterial hypertension. Other investigators (274-278) have demonstrated increases in cardiac output and arterial blood pressure following ICP elevation in association with no change or a decrease in peripheral vascular resistance.

Most likely a combination of these several mechanisms is responsible for the development of arterial hypertension following elevated ICP.

In our experimental investigations, using supratentorial extradural ICP monitoring and a constant insult infusion rate of approximately 1 ml/5 sec, we found, regardless of the volume or type of insult, that all groups demonstrated similar vasopressor responses to elevated ICP. Mean arterial blood pressure response times ("time to change") were similar as were the ICP levels at which MaBP started to respond. The peak MaBP responses were essentially identical. The MaBP "times to peak" were slightly shorter for the lower volume SAH groups and the artificial CSF group. Maximum ICP levels reached were similar for all groups, except for the 1.0 ml/kg SAH group in which ICP was lower than the rest. During the insult ICP was maintained approximately 10-20 mmHg below MaBP. The $\overline{\text{CPP}}$, calculated during the insult (until peak ICP value was reached) was similar for the larger volume SAH groups, the artificial CSF group and the SDHRx and SAHRx groups. For the lower volume SAH groups and the SDH groups, this value tended to be greater. The duration of MaBP elevation was greater for the larger volume groups, regardless of the type of insult. During ICP recovery $\overline{\text{CPP1}}$, was similar for all the groups in the study. The initial vasopressor responses for all the groups in our study were similar, despite different volumes and types of insult. With the infusion rate constant these responses were related only to the absolute ICP elevation, which was less than MaBP. The duration of MaBP elevation following completion of the insult was directly related to both the volume used, and to the length of time the ICP remained elevated.

Our findings are in agreement with several other workers who have also shown vasopressor responses at ICP elevations below diastolic or mean arterial blood pressure (219,247,248,262,263,279,280). Although our results conflict with Cushing's observations of a vasopressor response only when ICP approaches or equals the arterial blood pressure (38,222,259), we believe that his theory of arterial hypertension as a response to medullary anemia remains credible. As was documented in Chapter III (Results), $\overline{\text{CPP}}$ during the insult for all groups was lower than normal, and this possibly may have given rise to medullary ischemia. We also noted that during the insult induction, MaBP elevations appeared to try to stay ahead of increasing ICP levels, perhaps demonstrating an attempt to maintain medullary perfusion in the face of ischemia. This experimental finding has also been reported by Cushing (38,259) and Langfitt (248).

Bradycardia resulting from elevated ICP as reported by Cushing (38,222,259) has been observed both experimentally and clinically, but is not as regular an occurrence as arterial hypertension under the same circumstances. Other investigators (218,266,281), have found varying HR responses to increased ICP, including bradycardia, tachycardia, or no change at all. Similarly, patients with elevated ICP may present with various HR changes. In our investigations the general response of heart rate was bradycardia and other arrythmias and these will be discussed in a following section. Cushing (38) also reported that if ICP was increased slowly both HR and respiratory pattern remained unchanged. It is now generally accepted that depending on the rate and degree of ICP elevation, HR responses are variable but tend to bradycardia with rapid and high ICP elevations.

The reported initial respiratory responses to increased ICP are also variable. Various patterns of change of Vt and RR have been observed depending upon the rapidity and the degree of ICP elevation (38,216,218,219,259,281).

Our studies also showed that the respiratory pattern changes prior to the development of apnea were quite variable. Apnea subsequent to the insult was more frequent and prolonged in the higher volume groups. The total duration of apnea was directly related to the length of time that ICP remained elevated but not to either peak ICP or CPP.

Cushing (38) reported that if medullary anemia persisted, (ie failure of the vasomotor response to maintain adequate medullary perfusion in the face of elevated ICP) respiratory arrest occurred.

Other investigators have also shown the development of apnea subsequent to sustained ICP elevation in experimental animals (216,217,218,219). Recovery of respiration following apnea appears to be a function of the degree of trauma. With prolonged ICP elevations respiratory arrest does not recover (38,216,217,218,219).

In our studies those animals demonstrating persistent, significant ICP elevation did not recover from apnea. One animal in the 1.67 ml/kg SAH group, several in the SAHRx group and those animals receiving intracerebral hemorrhages did not recover from the apneic episode.

In spontaneously breathing experimental animals undergoing ICP elevations, death results from the development of respiratory arrest followed by cardiovascular decompensation (38,216,217,218,219). Steiner et al (216) performed repeated intracranial hemorrhages in dogs and demonstrated this sequence of events prior to death. When artificial ventilation was instituted vital functions recovered and the animals survived.

Clinically, respiratory failure, anticipating cardiac failure with subsequent demise following increased ICP, has been reported by many investigators (39,110,114,220,222,246). This sequence of events is frequently seen in neurosurgical units: the development of respiratory arrest with maintenance of HR and blood pressure. Survival of some of these patients is improved with mechanical ventilation. The 6 animals dying acutely in our investigations (4 in the SAH volume series, 2 in the SAHRx group) displayed respiratory failure followed by cardiovascular decompensation and death.

Apnea and respiratory failure developing from ICP increases most likely result from insults and damage to the respiratory centres. The degree of trauma to, and dysfunction of these centres is related to both the ICP increase and duration of its elevation. Recovery of respiratory function appears to depend upon the initial degree of intracranial trauma and the subsequent states of cerebral affairs (mainly cerebral circulation and ICP).

In our investigations, respiratory function recovered following the insult if cerebral circulation was maintained. On the other hand, those animals demonstrating respiratory recovery but persistently low CBF subsequently developed respiratory arrest and died. These observations show that respiratory embarassment subsequent to elevated ICP is reversible, but if further insult (low CBF) is added to the injury, respiratory failure occurs and death is inevitable.

Respiratory arrest subsequent to elevated ICP has been shown to recover with relief of the increased ICP (218,219,222,251,280).

In our studies we observed recovery of respiration following spontaneous reduction of ICP. Thus, the factors involved with respiratory dysfunction following intracranial insult appear to be the initial degree of trauma and subsequent status of the cerebral circulation and ICP. Combinations of these principal factors can lead to respiratory arrest with subsequent cardiovascular decompensation and demise.

The etiology of the cardiorespiratory response comprising the Cushing phenomenon following increased ICP remains controversial. Cushing (38) attributed these changes to medullary anemia. However, Thompson and Malina (280), in dogs, found that with the development of a pressure gradient between the supratentorial and infratentorial compartments, cardiorespiratory changes occurred at ICP levels below MaBP. They theorized that with the pressure gradient resulting from acute increases in ICP, and fixation of the neuraxis by the dentate ligaments, acute dynamic axial brainstem distortion results giving rise to the documented cardiorespiratory responses. If this distortion continues, respiratory arrest occurs, and is followed by decompensation and death. Thompson and Malina (280) also postulated that with distortion and buckling of the brainstem, basilar perforating vessels may be kinked and torn loose inside the stem, resulting in brainstem hemorrhages. Such a finding has been demonstrated by Johnson and Yates (36) in patients dying from intracranial space occupying lesions. Heck (249) agrees with the development of pressure gradients within the cranium, and attributes the cardiorespiratory changes to shearing stresses on neural structures.

Other investigators have studied the etiology of the vasopressor response following elevated ICP. Rodbard et al (282) elicited a pressor response with cerebral anoxia, and then demonstrated that a further vasopressor response could be superimposed upon that due to anoxia by increased ICP. These authors found that the response due to elevated ICP was faster in onset and of greater amplitude than the anoxic effect. They postulated the presence of intracranial baroreceptors (similar to the carotid sinus) that are responsible for the vasopressor effects. Taylor and Page (283) suggested that the pressor response following increased ICP was due to a combination of baroreptor and anoxic effects. McGillicuddy et al (284) demonstrated experimentally that cerebral ischemia as well as hypoxemia, without accompanying ICP elevation, resulted in a hypertensive response. They also showed that the hypertensive Cushing response was associated with increased ICP, and suggested that this was due to distortion and ischemia of brain stem areas. They felt that cerebral ischemia with attendant hypoxia may play a role in the classic Cushing response.

McDowall et al (262) defined these hypertensive responses to ICP increases (using an extradural ballon in dogs and baboons) as due to either (i) inadequate supratentorial perfusion pressure or (ii) torsion of the brainstem. Weinstein et al (247), using rhesus monkeys, found that the vasopressor response resulted from local pressure on, or ischemia of many parts of the central nervous system including the hemispheres, brainstem and spinal cord.

All of the above noted mechanisms have been shown to be involved in the development of Cushing phenomenon following ICP elevation. It is obvious that combinations of these mechanisms are involved in the production of the observed cardiorespiratory changes subsequent to ICP elevation.

In our investigations, as well as in those of other workers, failure of respiration antedates and appears to precipitate cardiovascular decompensation and death following increased ICP. These respiratory abnormalities are reversible if the insult was not too destructive, and are compatible with life as long as other physiological parameters are maintained. Adequate cerebral circulation following SAH is associated with respiratory recovery, whereas poor circulation is followed by respiratory arrest and death. Mechanical ventilation has been shown to improve cardiovascular status and survival. Prolonged ICP elevation is directly related to respiratory dysfunction, and reduction of ICP has been found to be associated with respiratory recovery. The prevention of further insult to and already compromised respiratory centre appears to be compatible with survival from SAH and other intracranial disorders associated with increased ICP.

CARDIAC RHYTHM AND EKG ABNORMALITIES

Electrocardiographic abnormalities occurring with subarachnoid hemorrhage were first described by Byer et al in 1947 (285). These changes consisted of upright T waves and prolonged Q-T intervals. Since that time, EKG pattern abnormalities and arrythmias have been found in association with the wide spectrum of cerebral disorders. Comprehensive reviews of EKG abnormalities associated with subarachnoid hemorrhage have recently been published by Weintraub et al (286) and Weidler (287).

The most common EKG abnormalities found in SAH in patients are depression or elevation of ST segments, prolongation of Q-T intervals, T wave inversion, upright T waves and prominent u waves, exhibiting evidence of cardiac ischemia and infarction (288,289). The most frequent arrythmias associated with this disorder include sinus bradycardia, junctional rhythms, A-V dissociation, A-V block, atrial premature beats, wandering atrial pacemaker, idioventricular rhythm, ventricular premature beats, ventricular tachycardia and ventricular fibrillation (289,290). The various EKG abnormalities exhibited by the experimental animals in our investigations, during and immediately following intracranial insult, were essentially the same as those described in clinical SAH. There were essentially no differences in the EKG pattern abnormalities or the arrythmias experienced by the various groups receiving an intracranial insult.

In general, the EKG changes noted in our studies reverted to normal within 10 minutes of the insult, whereas in patients suffering SAH, the abnormalities have persisted for hours to days after the hemorrhage. Similar to our findings, Estanol et al (291), following SAH in dogs, found the development of arrythmias including sinus bradycardia, premature ventricular beats and ventricular tachycardia within 1-3 seconds of the hemorrhage and lasting up to 3-4 minutes.

Since the discovery of the association of EKG abnormalities with intracranial disorders there has been a great deal of investigation into their etiology. Both the sympathetic and parasympathetic nervous systems have been implicated. The increased sympathetic and parasympathetic activity subsequent to cerebrovascular accidents have been designated by some investigators as direct causes of the resultant EKG changes (287,289-294). Manning et al (293) state that increased sympathetic drive causes a nonuniform increase in the excitability of ventricular muscle by decreasing the refractory period, and the increased parasympathetic outflow depresses the firing rate of the automatic atrial cells. Under these 2 conditions a myriad of arrythmias is possible. Alterations in ST segments and T waves are explained on the basis of nonuniform changes in the refractory periods resulting from sympathetic stimulation.

Other observers attribute the changes in EKG rhythm and pattern due solely to one or the other of these 2 systems; sympathetic (288,295,296) parasympathetic (297,298,299). The abnormalities are due to either (i) changes in the electrical properties of cardiac muscle, or (ii) damage to the myocardium.

In 1964, Koskelo et al (300) reported left ventricular subendocardial petechial hemorrhages in the hearts of 3 patients with EKG abnormalities dying of SAH. Greenhoot et al (288) hypothesized that the massive sympathetic discharge following SAH was responsible for the release of catechloamines locally in heart tissue causing cellular damage and myocardial necrosis, which in turn gave rise to EKG abnormalities. They showed that the area of the cell injured was adjacent to the nerve terminal and attributed the damage to the metabolic effects of norepinephrine on cardiac cells. The subendocardial necrosis in their experimental rats was similar to that found in humans dying from SAH. An interesting finding in Greenhoot's studies was the development of pulmonary edema in 2 animals. Greenhoot et al (288) referred to Ducker's work on pulmonary edema (301) and stated that if the cardiac damage was sufficient, left ventricular failure would ensure, followed by pulmonary edema (to be discussed more fully in the section on pulmonary edema). Cruickshank (295) stated that in patients with SAH, EKG abnormalities resulted from sympathetic stimulation and circulating adrenal catecholmines. He theorized that increased circulating corticosteroids deplete myocardial intracellular potassium potentiating the cardionecrotic effects of catecholamines. Manning et al (293) do not agree with the association of EKG abnormalities during life and postmortem cardiac changes. They feel that the subendocardial hemorrhages resulted from the massive sympathetic discharge occurring at the terminal stage. Thus it is felt that EKG changes can occur with a normal heart, and on the other hand, the EKG could remain normal despite myocardial damage (if not very extensive).

Cropp and Manning (297) suggested that the EKG abnormalities seen in patients with intracranial hemorrhages are due to vagal activity resulting from stimulation of the frontal lobe (area 13) and anterior cingulate gynus (area 24). Shuster (299) supports the parasympathetic system as the responsible factor for EKG changes with SAH. He was able to abolish the S-T segment changes with intravenous atropine.

Arseni et al (298) postulated that with increased ICP, vagal hypertonicity caused bradycardia and other EKG changes. They also felt that with the systemic hypertension following elevated ICP left ventricular pressure increased resulting in local anoxia of the subendocardial layer. If this state persisted subendocardial hemorrhages would occur, and these are demonstrated by EKG irregularities of the ischemic type. This finding is also supported by Koskelo et al (300).

Hawkins and Clower (294) reported that both the sympathetic and parasympathetic nervous systems and circulating adrenal catecholamines were involved with the production of myocardial damage resulting from intracranial hemorrhage. Using mice, they found that the incidence of myocardial damage resulting from intracranial hemorrhage was reduced by separately blocking each of the aforementioned systems i.e. pretreatment with reserpine, atropine and adrenalectomy.

Offerhaus et al (302) using rabbits, found EKG changes following SAH similar to those seen in humans. However, no myocardial abnormalities were observed. They also found that the myocardial tissue catecholamine concentration was increased, and that of the adrenals decreased following the insult. Increased plasma epinephrine and norepinephrine after SAH in dogs has been documented by Boddin et al (303). Peerless et al (269) and Benedict et al (270) have found elevated plasma catecholamine levels in humans following SAH. Offerhaus et al (302) were able to abolish post-SAH EKG changes by post-insult administration of propanalol, demonstrating that catecholamines were involved in causing these changes. Vagotomy had no effect.

EKG abnormalities and myocardial damage are definitely associated with intracranial hemorrhages, most likely through the effects of increased ICP. The autonomic nervous system and circulatory catecholamines have been implicated as direct causes of these changes. Clinical implications are that the myocardial damage and EKG abnormalities may play a role in the mortality resulting from SAH. Furthermore, delay of definitive aneurysm surgery in SAH patients because of arrythmias and other EKG irregularities may allow time for rebleeding. Patients with intracranial hemorrhage should be monitored for EKG abnormalities, and if present, treatment should be considered. The problem arises whether the treatment should entail beta adrenergic blocking agents alone, or these agents with atropine. Secondly, these drugs may adversely effect the systemic and cerebral circulations with resultant additional complications. Further investigation is needed to elucidate the clinical consequences of these EKG abnormalities, as well as the benefits and adverse effects of possible therapies.

Another problem is that transplantation donors with intracranial pathology may have damaged hearts which are unsuitable for transfer (304). This is another indication for close cardiac monitoring of patients with cerebrovascular and other intracranial disorders.

RESPIRATORY PATTERN AND PULMONARY CHANGES

The larger SAH volume groups, the artificial CSF group and the treatment groups all demonstrated increased Vt in association with decreased or normal RR on recovery of respiration following the insult-induced apnea. Accompanying these changes, PaCO2 was reduced, A-aDO2 increased and there was an initial minimal reduction in PaO2.

Hyperventilation persisted throughout the experimental investigations, but not to the degree noted in the first 10 minutes of respiratory recovery. The largest increases in A-aDO2 and greatest decreases in PaO2 were present approximately 15 minutes following the most marked degree of hyperventilation (lowest PaCO2). Throughout the experimental studies, there was some improvement in both A-aDO2 and PaO2, but the abnormalities persisted. All groups demonstrated an increase in pH at the time of maximum hyperventilation. During the rest of the study, the pH of the larger SAH volume groups remained lower, and that of the artificial CSF group slightly higher than normal. For the SAHRx and SDHRx groups, pH tended to remain elevated. For the Rx alone group pH remained unchanged during the major part of the studies but tended to increase towards the completion.

Changes in respiratory pattern, consisting of increased minute ventilation and decreased PaCO2, have been documented following acute increases in ICP from various causes ranging from cerebral trauma to spontaneous intracranial hemorrhage (38,182,201,205,210,213,222,259,305,306). The etiology of hyperventilation in patients with head injuries has been attributed to central neurogenic mechanisms associated with hemorrhages and other lesions of the midbrain and brainstem (182,201,212,215). Hypoxemia is also known to cause hyperventilation. However, in our investigations, hyperventilation was at its maximum prior to the largest observed reduction in PaO2. Relative hypoxemia persisted throughout the studies and this may have been a factor contributing to PaCO2 reduction during this period. Froman et al (306) found in his series of patients with intracranial hemorrhage that CSF pH was low and blood pH high. They felt these findings due to the metabolism and breakdown of blood in the CSF and postulated that the acidity was the cause of the ensuing hyperventilation. It is also possible that the initial hyperventilation subsequent to the insult, if persistent, causes a reduction in CSF bicarbonate with resultant acidity that will perpetuate the increased minute ventilation (307). Froman (205) reported that the respiratory aberrations observed resulted from altered cerebral blood flow and metabolism. In our investigations also, hyperventilation did not correct the observed hypoxemia. Thus, the reduction in PaO2 was not the sole cause of the increased ventilation. The lack of PaO2 correction during hyperventilation indicates that the hypoxemia resulted from problems of adequate oxygenation.

Several investigators (305,306) reported a persistently elevated blood pH, whereas we did not find such a consistent pattern. Some of our groups had normal, some decreased, and some elevated pH values following the insult. A possible explanation for this discrepancy is the development of varying degrees of lactic acidosis due to shunting of blood from the periphery with resultant anaerobic metabolism such as described by Berman (208). Lactic acidosis may have negated the respiratory alkalosis thus giving rise to the various pH patterns observed. Blood lactate levels, however, were not measured in our investigations.

From our experiments, it is clear that the degree of respiratory pattern changes and hypocarbia are related to both the volume of the insult, and to the fluid medium used. The lower volume SAH groups did not experience hyperventilation nor respiratory pattern abnormalities to the degree seen in the larger volume groups. The ICP responses of all 4 SAH volume groups were similar except for the ICP in the larger volume groups taking longer to peak and to be elevated for a longer period of time than was the case in the lower volume groups. Despite these ICP differences, CPP during elevated ICP was not significantly different between the 4 volume groups. ICP elevation for a longer period of time may indicate a greater degree of cerebral insult, giving rise to greater respiratory abnormalities. Furthermore, the artificial CSF group experienced Vt increases and hypocarbia, but not to the extent of the same volume SAH group. The ICP responses to the insults in these 2 groups were similar, except for the longer duration of ICP elevation in the SAH animals. This again may be considered as a greater degree of cerebral trauma. Another observed difference was the presence of blood in the CSF which might have been responsible for the respiratory pattern abnormalities, resulting either from the effect of metabolic breakdown products or simply from an irritative effect of blood on the respiratory centres (306).

It has been shown that the greater the respiratory irregularities following intracranial insult, the poorer the outcome (182,211,215). Our results are in general agreement with this finding. The larger volume SAH groups and the SAHRx group (with greater respiratory changes) tended to do poorly whereas the lower volume SAH groups and the artificial CSF group fared well. The SDHRx group experienced respiratory changes and levels of hypocarbia similar to those of the SAH groups which had a poor outcome. In general, the SDHRx animals survived well despite the respiratory abnormalities. Thus, it is obvious that other factors are involved in the final outcome of intracranial hemorrhage, viz. subarachnoid blood, rCBF and hypoxemia, as well as other, as yet undetermined factors.

From our investigations the degree of trauma, manifested by the volume and type of injectate, dictates the degree of respiratory abnormalities resulting from the insult. The etiology of these changes could possibly include all of the previously described theories - medullary and brainstem insult, hypoxemia and ischemia, CSF acid-base imbalance.

Subsequent to the insult (within 8 minutes), hypoxemia and increased A-aDO2 values were found in the larger SAH volume groups and the SAHRx and SDHRx groups. The greatest decrease in PaO2 and increase in A-aDO2 in the SAH volume groups were demonstrated at the second post-insult CBF determination (22 minutes post-SAH). At this time in the treated groups the therapeutic regime was being instituted and arterial blood gas analysis and A-aDO2 calculation were not performed. It is most likely that similar changes in these parameters occurred at this time for the treated groups. All of these 4 groups experienced hypoxemia following the hemorrhage that gradually recovered to normal, or near normal levels, signifying relative hypoxemia, during the latter part of the investigations. A-aDO2 of the 2 treated groups and the 1.67 ml/kg SAH group remained elevated following the insult. As noted Chapter III (Results), the changes in PaO2 and A-aDO2 exhibited by the 2.0 ml/kg SAH group were heavily biased by the changes demonstrated by the acutely dying animals. For the 3 surviving animals PaO2 and A-aDO2 were normal.

The smaller value SAH groups and the artificial CSF group demonstrated decreases in PaO2 and increases in A-aDO2; these changes however, were not as significant, or as persistent as those demonstrated by the other groups. Towards the completion of the studies the Rx alone group developed a small degree of hypoxemia and minimal A-aDO2 elevation. This may have resulted from atelectasis known to occur during long periods of amaesthesia in spontaneously breathing animals.

Postmortem examination revealed the presence of varying degrees of pulmonary edema in those animals exhibiting large changes in PaO2 and A-aDO2 subsequent to the insult. Hypoxemia, arterial oxygen desaturation and elevated A-aDO2 have been documented in patients with elevated ICP resulting from intracranial disorders ranging from subarachnoid hemorrhage to cerebral trauma (180,182,191,202,204,205,210). Similar results have been obtained in experimental animals with artificially elevated ICP (206,208,209,305,308).

Nothnagel, in 1874 (309) noted the development of pulmonary edema and death following probing of the brain of a rabbit at unspecified areas. Moutier, in 1918 (178) observed the occurrence of fatal, acute pulmonary edema after cerebral trauma obtained in battle. The association of pulmonary edema with central nervous system injuries is now widely accepted. Weisman (189) found at postmortem examination of 686 cases of intracranial hemorrhage (spontaneous and traumatic) that 2/3 of them demonstrated pulmonary edema and congestion. He also reported that pulmonary edema occurred within 30 minutes of the insult. Simmons (184) performed autopsies on Vietnam casualties dying of various types of head injuries and found pulmonary edema, congestion and hemorrhage in the majority of cases studied. Seventeen of 20 patients dying within minutes of the intracranial trauma had developed pulmonary edema. Both of these observers commented that the resultant effects of pulmonary edema contributed to the mortality of these patients. Other investigators have reported similar findings of pulmonary edema in patients with intracranial disorders and increased ICP (182,183,184,191,202,210,310). In general, the belief is that the effects of this form of pulmonary edema are contributing factors to the demise of the patient.

This form of pulmonary edema is characteriesed by vascular congestion, and interstitial and intra-alveolar protein-rich edema fluid and hemorrhage; it has been called "neurogenic pulmonary edema" (NPE) to distinguish it from other forms of pulmonary edema. Depending upon the degree of edema, the normal ventilation-perfusion relationship is disrupted (physiological shunting) giving rise to varying levels of hypoxemia and elevated A-aDO2.

With respect to the etiology of NPE, several investigators (196,311) have postulated the presence of a hypothalamic "edemagenic centre" just posterior to the preoptic region, the activity of which is normally inhibited by adjacent structures including the preoptic nuclei. On release of this inhibition, by preoptic lesions, the development of pulmonary edema in rats has been demonstrated. It is postulated that this "edemagenic centre" is responsible for increased sympathetic outflow to the splanchnic nerves. This results in constriction of visceral venous reservoirs giving rise to a shift of bloood volume from the systemic to the pulmonary circulation, subsequently causing pulmonary edema. This pattern of events can be prevented by sympathetic pathway destruction with cervical cord section at C8 (196,311).

Reynolds (179) reports similar findings but discounts the release of inhibition of this centre, and postulates that stimulation of this "edemagenic centre" was responsible for the edema. Richards (312), in a postmortem series of 88 patients with intracranial lesions, found pulmonary edema in 52.3% of the cases; no specific cerebral lesion was found in association with the pulmonary edema, (including the anterior hypothalamic area). Richards also reported that histological study of the anterior hypothalamic region in 106 consecutive patients with ruptured intracranial aneurysm failed to reveal any consistent lesions associated with pulmonary edema.

Campbell et al (308,313) demonstrated that the occurrence of acute pulmonary edema in guinea pigs and dogs subsequent to increased ICP could be prevented by the administration of atropine following the insult, as well as by bilateral cervical vagotomy prior to the ICP elevation. They postulated that the subsequent increased vagal tone following increased ICP causes bradycardia and decreased cardiac output, with resultant increased pulmonary venous pressure. Pulmonary edema would then result from the increase in pulmonary capillary filtration pressure. Campbell et al (308,313) also noted that only 50% of the experimental animals with elevated ICP developed pulmonary edema.

Cameron and De (314) demonstrated in rabbits and rats the development of pulmonary edema with intracisternal injections of fibrin. Vagotomy prior to the insult prevented the edema. They postulated that the irritative effect of fibrin stimulated the dorsal vagal nucleus, and the resultant increased vagal tone was responsible for increased pulmonary capillary permeability and subsequent edema.

Other investigators have not substantiated the role of the parasympathetic nervous system in the development of the pulmonary edema associated with intracranial disorders. In fact, Farber (315) has demonstrated that sectioning of the vagi resulted in pulmonary edema in rabbits and guinea pigs. He felt this to be the result of redistribution of pulmonary hemodynamics subsequent to vagotomy. Mackay (194) found similar results following cervical vagotomy in guinea pigs.

Observers in both the clinical and experimental fields implicate increased sympathetic outflow and the Cushing response following increased ICP as responsible for the development of pulmonary edema (183,184,190,191,195,198, 199,200,208,209,316,317,318). The generally accepted theory is that increased ICP gives rise to a massive sympathetic outflow originating from the hypothalamus. The consequences of this are peripheral (including venous capillary bed constriction (266)) and visceral vasoconstriction (38,259) resulting in an increase of central core blood volume and a positive inotropic effect on the heart, giving rise to an increase in arterial blood pressure and cardiac output. With this increased load on the left ventricle, there is a shift of circulating blood volume from the systemic to the pulmonary circulation with associated marked increases in left atrial and pulmonary venous and arterial pressures. As a consequence, the increase in pulmonary capillary pressure surpasses the plasma oncotic pressure with resultant transfer of fluid into the interstices and alveoli of the lungs, and subsequent development of pulmonary edema. Some workers have postulated a "transient" left ventricular failure due to the increased left ventricular systolic and diastolic load (183,193,301,316). Others have described inadequate left ventricular relaxation caused by the sympathetic mechanism resulting in relative left heart failure as responsible for the increased pressure in the pulmonary circulation (317).

The role of the sympathetic nervous system in the production of NPE has been substantiated by its prevention and abolition using alpha adrenergic blocking agents, ganglionic blocking agents, general anesthetics, narcotic sedatives and cervical cordotomy (194,195,209,311,316,317).

Hessler and Cassin (319) found no increase in pulmonary venous pressure with increased ICP in goats, but did find elevated pulmonary arterial pressure and increased pulmonary vascular resistance. They postulated active pulmonary vascular constriction due to the sympathetic discharge. Malik (207) and Moss et al (305) have reported similar conclusions from their experimental investigations. Hessler et al (319) and Malik (207) found that alpha adrenergic blockade with phenoxybenzamine prevented the increases in pulmonary vascular resistance and pulmonary artery pressure.

The occurrence of pulmonary edema with elevated ICP is well known. The participation of the sympathetic nervous system in its development is accepted by most investigators. The mechanisms involved are thought to be overloading of the pulmonary circulation, and possibly elevated pulmonary vascular resistance resulting from pulmonary vasoconstriction of sympathetic origin.

Our investigations revealed that the length of time the right ventricular pressure remained elevated above resting was directly related to the degree of hypoxemia and A-aDO2 elevation. These parameters in turn, were directly proportional to the severity of pulmonary edema found at postmortem examination. The absolute RVP increase was not related to either PaO2 or A-aDO2 changes or to the degree of pulmonary edema. Ducker (198) reported in his experiments with dogs, that not all experimental animals developed pulmonary edema following increased ICP. Specifically, only those animals that experienced marked elevations in pulmonary venous and arterial pressures developed edema. In these studies, the pulmonary venous pressure initially exceeded that of the pulmonary arterial pressure, supporting the theory of pulmonary circulation overload.

Similarly, not all of our experimental animals developed pulmonary edema. Within individual groups of animals all experiencing the same ICP patterns, some developed greater RVP changes resulting in edema and its consequences, than did others. The discrepancies of the RVP responses under the same circumstances in different animals remain unexplained at present.

We are in agreement with reports that have demonstrated and postulated that pulmonary edema arises from increased pulmonary capillary pressure exceeding that of the plasma oncotic pressure with subsequent movement of fluid into the pulmonary interstices and alveoli (183,184,190,195,198,199, 208,209,316,317,318)

Some of the experimental animals in our study developed hypoxemia and elevated A-aDO2, but were found to have only minimal, or no pulmonary changes at postmortem. A possible explanation for this finding (as has been shown by Ducker (183)) is the resolution of pulmonary edema with a return of function to normal following relief of elevated ICP. Berman (209) demonstrated the development of hypoxemia in dogs following increased ICP, without pulmonary edema. He postulated that this resulted from the opening of anatomical shunts subsequent to the increased pulmonary circulation. Poor oxygenation of blood would then occur due to ventilation-perfusion abnormalities subsequent to the shunting. Another possibility is the presence of minimal degrees of pulmonary edema, not observed at histological examination, and yet enough to cause ventilation-perfusion defects because of poorly ventilated alveoli (physioloigical shunt) resulting in hypoxemia and elevated A-aDO2.

The artificial CSF group did experience mild changes in PaO2 and A-DO2, but these were not persistent, and the lungs were normal at postmortem examination. The ICP and RVP were elevated in this group for a shorter period of time than in its SAH counterpart. These changes in PaO2 and A-aDO2 may have been due to ventilation-perfusion abnormalities that did not persist (209) or to pulmonary edema that resolved (183). This sequence of events has also been found by Maxwell (180) who reported relief of hypoxemia following return to normal of ICP.

Thus, on the basis of our results, the severity of pulmonary changes both physiological and pathological are related to the degree of trauma (duration of ICP elevation). This has also been shown by Maxwell (180). The longer the ICP remains increased above normal, the longer the RVP stays elevated, resulting in greater degrees of pulmonary edema, hypoxemia and A-aDO2 elevation.

Our investigations are in general agreement with others in this field. Elevated ICP is associated with systemic hypertension, right ventricular hypertension (indication of pulmonary arterial systolic hypertension), pulmonary edema, hypoxemia and elevated A-aDO2.

In 5 of the 6 animals dying acutely in both major investigations, A-aDO2 was elevated to a greater extent than that of the experimental animals surviving the duration of the experimental period. We also found that the experimental animals experiencing larger increases in A-aDO2, with greater degrees of hypoxemia, and with documented pulmonary edema at postmortem, fared worse following the intracranial insult than did those without such marked changes. These animals belonged to the larger SAH volume groups and the SAHRx group. The experimental animals in the SDHRx group demonstrated PaO2, A-aDO2 and pulmonary changes similar to those seen in the larger volume SAH groups and in the SAHRx group, however they survived the insult much better. Thus, the pulmonary changes associated with intracranial hemorrhage no doubt play a role in the resultant poor outcome, but there are other contributing factors including: CBF, cerebral metabolism and blood in the subarachnoid space.

Various treatments of NPE have been suggested from both clinical and experimental studies in an attempt to improve pulmonary function. Alpha adrenergic blockade has been effective experimentally in preventing the development of pulmonary edema (184,193,194,195,207,209,319). However, in these particular experiments, the drugs were administered prior to the insult. The effectiveness of these agents when administered after edema has already developed remains to be investigated. Similarly, ganglionic blockers have been effective as pretreatments in preventing NPE (195). Beta adrenergic blockers have been found to aggravate the edema or to have no effect at all (207,209,319). At present, the only treatments directed towards improving post-insult pulmonary function include artificial ventilation if respiratory difficulty is present, proper tracheal care if an endotrachial tube is in place and assured adequate arterial oxygenation.

Positive pressure ventilation has been suggested as an effective means of reducing the edema, as has been positive end expiratory pressure (PEEP) (182,183). PEEP has also been shown to improve oxygenation in patients with NPE (186,201). Ducker (183) has demonstrated that ICP reduction results in relief of pulmonary edema. Maxwell (180) showed improvement in oxygenation with ICP reduction. The present work indicates that significant efforts should be made to reduce elevated ICP in order to both improve pulmonary function and prevent further or continuing cerebral insult. General anesthetic agents and narcotic sedatives have been used effectively in experimental animals to prevent NPE both by their CNS depressive effect and by non- specific reduction of the sympathetic discharge (193,195). These agents have also been shown to reduce elevated ICP, and may improve NPE through this mode. The use of such agents in patients that are already in a compromised neurological state remains questionable.

Other problems involved in the treatment of NPE using a drug regime include the possible cardiovascular and cerebrovascular effects which may disturb the regulatory mechanisms maintaining adequate cerebral circulation, or disrupt an already compromised circulation.

Development of neurogenic pulmonary edema with hypoxemia and elevated A-aDO2 is one of the principal factors involved in determining the outcome following SAH. Despite apparent experimental success in preventing edema subsequent to ICP elevation, no therapeutic regime has been effective clinically in improving pulmonary function once NPE has developed.

CEREBRAL CIRCULATORY DISTURBANCES

Evidence of a good experimental preparation in our investigations was provided by the stability of the measured parameters prior to the insult, i.e. during the first 4 CBF determinations. Regional cerebral blood flow was measured using the intra-arterial 133 Xenon clearance technique of Lassen et al (233). The method adopted for the calculation of these values was the so called "initial-slope-index", and these values were not corrected for PaCO2.

Subsequent to the insult, in each of the 4 SAH volume groups, there was a reduction in rCBF (significant in groups 1.0, 1.67 and 2.0 ml/kg). This rCBF reduction was accompanied by a decrease in CPP (significant for groups 1.33, 1.67 and 2.0 ml/kg). The artificial CSF group showed a significant decrease in rCBF following the injection, but CPP remained normal. All of these 5 groups showed an increase in calculated CVR but this was significant only for the artificial CSF group.

The magnitude of the rCBF reduction at this first post-SAH measurement tended to be greater for the larger SAH volume groups compared to the smaller volume groups. Similarly the rCBF decrease of the 1.67 ml/kg SAH group was greater than that of the artificial CSF group.

The CPP reduction of the 4 SAH volume groups was in the main secondary to a decrease in MaBP and not to ICP elevation. Relative CPP decrease and CVR increase were greater for the larger SAH volume groups. For the artificial CSF group, CPP remained unchanged and the CVR increase was smaller than that of its SAH counterpart.

Following the insult, ICP in the larger volume SAH groups remained elevated for a longer period of time than did the ICP of the other 3 groups in the first major investigation. CPP during the period of elevated ICP was similar for all of these groups, but due to the longer duration of increased ICP, CPP was compromised for a longer period of time in the larger SAH volume groups.

Reduction of CBF during the acute stages of SAH has been well documented both clinically (55,56,57,59,80-92) and experimentally (66,67,70,74,76,78,94-99).

Following the acute stage in our studies rCBF in the lower volume SAH groups recovered; the 1.33 ml/kg SAH group returning to normal, the 1.0 ml/kg SAH group to a slightly sub-normal level. The CPP during the studies demonstrated improvement following the initial decreases in these 2 groups. However, CPP recovery of the 1.33 ml/kg SAH group was more complete than that of the 1.0 ml/kg SAH group. Despite CPP recovery to normal in this latter group, rCBF remained lower than the pre-SAH control levels (significant at CBF 7,8). The CVR of this group was elevated for the duration of the studies, whereas that of the 1.33 ml/kg SAH group was normal, or slightly less than pre-insult levels.

For the 2 larger volume SAH groups, rCBF remained lower than resting levels for the duration of the studies. The CPP in the 1.67 ml/kg SAH group recovered to near normal limits. Similarly, CPP of the 2.0 ml/kg SAH group recovered but then fell again towards the end of the investigations, but the decrease was not significantly lower than normal. For the 1.67 ml/kg SAH group, CVR remained elevated, and that of the 2.0 ml/kg SAH group was increased up until CBF (7), after which it was normal. The reason for this, as previously noted in the Results section was that the 2 acutely dying animals in this group had marked CVR elevations. The remaining 3 experimental animals had normal CVR. Thus, following the demise of the former 2 animals, CVR of the 2.0 ml/kg SAH groups was normal.

In the artificial CSF group, CPP was normal, rCBF remained minimally decreased and CVR slightly elevated.

During our studies, in the post-insult period, there were only minimal changes in PaCO2 from resting levels in the lower volume SAH groups and the artificial CSF group. Calculations of rCBF using PaCO2 correction factors demonstrated that the CBF reductions in these groups were due to the effects of the insult and not due to changes in PaCO2. There were greater PaCO2 reductions in the larger SAH volume groups, especially at CBF (5,6). These changes did result in CBF reductions, but CBF calculations, using correction factors for PaCO2 levels showed that, in association with the rCBF decrease due to PaCO2 reduction, rCBF was diminished due to the effects of the hemorrhage. Following CBF (6), PaCO2 improved to near normal, but rCBF remained low. Thus, hypocapnia following the insult is responsible in part for rCBF reduction, but the major part of the observed decrease results from the intracranial insult.

We were able to document the following findings:

(i) larger SAH volume groups demonstrate rCBF reductions that are initially greater, and are of longer duration than for the lower volume groups. Similarly, CVR elevations are initially greater, and are of longer duration in the large volume groups.

(ii) the rCBF decreases immediately following the hemorrhage were accompanied by decreases in CPP, as well as marked increases in CVR, indicating that rCBF was reduced by both reduction of CPP and elevation of CVR.

(iii) rCBF remained lower than normal despite normal or near normal CPP during our studies. This reduction in rCBF would then necessarily result from increased CVR (CBF = CPP/CVR).

(iv) rCBF in the artificial CSF group was slightly reduced despite normal CPP. This reduction was associated with increased CVR.

(v) the PaCO2 decreases seen subsequent to the insult did cause some rCBF reduction, especially in the larger SAH volume groups at CBF (5,6), but the greater part of the rCBF decrease was due to the intracranial effects of the insult.

Reduction of CBF, both global and regional following SAH experimentally (66,67,70,76,96,97,98,100) and clinically (55,56,57,59,61,62,81,82,85,88,90,92,93,99) is now widely accepted. Kelly et al (60) using dynamic brain scanning found that post-SAH patients had reduced cerebral perfusion. Other investigators (87,91,320) found increased cerebral blood circulation times in patients with SAH. On the other hand, Steiner et al (321) found that CBF remained normal in dogs during the SAH and for 2 hours following the hemorrhage. Our results are in general agreement with those studies showing reduced CBF following SAH.

The various etiologies of reduced CBF following SAH include:

(i) autoregulatory disturbances.
(ii) autonomic nervous system, stimulation or distruption.
(iii) cerebral vasospasm.
(iv) microcirculatory disturbances.
(v) metabolic changes.

Autoregulation is the term applied to the mechanism by which CBF remains constant despite changes of perfusion pressure (102). This type of "autoregulation" of CBF is accompanied by changes of CVR, and is due to alterations of the caliber of regulatory cerebral arterioles (322,323). Experimentally, autoregulation has been shown to remain intact to CPP levels as low as 35-40 mmHg. ICP elevation in these studies was by infusion of artificial or mock CSF and of Ringer's lactate into the cisterna magna and lumbar subarachnoid space (102,108,118,122,243,324). Matakas et al (121) found that autoregulation was lost in rhesus monkeys with a CPP less than 50 mmHg when raising ICP by infusion of isotonic saline into the parietal subarachnoid space. Symon (109) reported autoregulatory failure when the ICP was raised to 70 mmHg, in baboons, with Ringer's lactate infusion into the cisterna magna.

Jennett et al (122) have shown that reducing CPP by lowering the blood pressure was associated with intact autoregulation down to a level of 35-40 mmHg. Miller et al (102) demonstrated that there was a failure of autoregulation following blood pressure reduction to CPP levels of 40-50 mmHg. They also noted that autoregulation was more effective if CPP was lowered by increasing the ICP rather than reducing the blood pressure. Olesen (325) demonstrated that CBF in humans remains constant until MaBP is decreased to between 50-70 mmHg.

These investigations were carried out in otherwise normal experimental animals, and in essentially normal patients. From our results, the rCBF reduction seen in the SAH volume groups was initially (at least) accompanied by a reduction in CPP thus indicating impaired autoregulation. This initial CPP reduction was due to both an increase in ICP and a decrease in MaBP, but in general, the latter was the more prevalent cause of decreased CPP. During the ensuing investigations, in the lower SAH volume groups, CPP tended to recover. In the 1.0 ml/kg SAH group, CPP returned to normal, and rCBF remained low. This indicates an increase in CVR. For the 1.33ml/kg SAH group, rCBF returned to normal, whereas CPP remained low, demonstrating intact autoregulation. In the larger volume groups, CPP remained below resting levels as did rCBF. In these groups, autoregulation was impaired, and remained so for the duration of the studies. In association with impaired autoregulation, CVR was increased. Thus, the etiology of reduced rCBF post-SAH from our investigations includes both impaired autoregulation and increased cerebrovascular resistance, the degree of which is greater for those groups receiving larger SAH insults.

Autoregulation has been found to be impaired following cerebral trauma (239,326,327), SAH (59,81,328), cerebral hypoxia (329,330), cerebral ischemia (104,105,331) and cerebral compression (117). In patients, following SAH, Heilbrun et al (81) found a decrease in CBF and demonstrated loss of autoregulation, which they felt resulted from cerebral tissue hypoxia and acidosis. Fieschi et al (104) showed, in patients with ischemic cerebral lesions, decreased rCBF, and impaired autoregulation to elevated blood pressure which they believed to be due to tissue posthypoxic acidosis. Bruce et al (239) found in patients (mostly with head injuries) that autoregulation was impaired and that CBF tended to remain low. This was true of patients with and without mass lesions. They found that with mass lesions, autoregulation was impaired over and adjacent to the lesion, and was intact in the rest of the cerebral hemisphere. In their study, the reverse was also seen. Bruce et al (239) suggested that focal edema may decrease CBF through compression of the microcirculation, and showed CBF to increase following the administration of mannitol.

Experimental investigations have shown autoregulation to be impaired following induced SAH in baboons (100,328), monkeys (67,99), and cats (94). Hashi et al (100,328) demonstrated an increase in CBF immediately following SAH, and that autoregulation was impaired only when CPP was decreased. However, 24-48 hours post-insult, CBF was reduced and autoregulation was totally impaired. Yamaguchi et al (94) and Fein (99) reported a decreased CBF and disturbed autoregulation following induced SAH in experimental animals.

Various theories have been proposed for the failure of autoregulation under the previously described circumstances. Langfitt (117) has proposed vasoparalysis of the cerebral vessels resulting from ischemia. This idea has been supported by other investigators (102,109) who postulate that ischemia leads to tissue hypoxia and acidosis resulting in vasoparalysis (59,81). Others have presented evidence that failure of autoregulation occurs because maximal vasodilatation of the resistance vessels has already occurred (104,109,328). Zwetnow (108) has shown that the cerebral metabolic-flow coupling relationship is disturbed at low CPP levels. Fein (99) postulated that SAH interferes with this coupling mechanism. At present, the evidence indicates that the mechanisms involved in maintaining adequate cerebral perfusion (autoregulation) are disturbed following SAH. The etiology of the disruption is generally believed to be involved with the cerebral metabolic changes subsequent to the insult, most likely resulting from tissue hypoxia and acidosis due to ischemia.

Associated with, and as a result of disturbed autoregulation, is the "luxury-perfusion syndrome" or hyperemia found both clinically (104,332,333) and experimentally (102,108,118) in severe brain damage. Miller et al (102) showed, in dogs, that with impaired autoregulation, CBF was higher than normal, despite low levels of CPP. We did not find any evidence of increased rCBF or hyperemia following SAH in our investigations either with low or normal CPP values.

As has been previously documented, our results indicate impaired autoregulation in the larger SAH volume groups. Langfitt et al (117) showed by experimentally increasing ICP in rhesus monkeys with a supratentorial extradural balloon, that more rapid and higher ICP elevations were associated with greater decreases in CBF and larger degrees of vasoparesis. Similarly we have demonstrated larger rCBF reductions and greater degrees of autoregulatory impairments in the larger SAH volume groups. These groups experienced longer durations of ICP elevation following the insult than did the lower volume SAH groups or the artificial CSF group. Thus, longer periods of ICP increase are associated with greater reductions in rCBF and greater impairment of autoregulation. This is demonstrated by the recovery of rCBF and autoregulation in the 1.33 ml/kg SAH group despite a low CPP, as opposed to the persistent rCBF reduction and longer period of impaired autoregulation in the larger volume groups.

In addition to the loss of autoregulation as a cause of reduced rCBF in our experiments, we also found increases in CVR. This indicates that the loss of autoregulation was not the only cause of decreased rCBF following the SAH. Greater increases in CVR were present in the larger SAH volume groups than in the smaller ones. The artificial CSF group showed a slight elevation in CVR in association with minimally decreased rCBF immediately following the insult.

The cerebral arterial circulation is supplied by 2 major types of vessels: (i) the larger superficial or conductance arteries and (ii) the smaller nutrient or penetrating vessels (334). These smaller vessels and their ramifications are considered to be the resistance vessels regulating cerebral blood supply. The larger conducting vessels generally function as a pressure head reservoir assuring adequate perfusion for the smaller vessels (335). However, it is felt, following SAH and the development of vasospasm, that the reservoir function is lost and these larger conducting vessels function as a resistance system (336).

Since the first documentation of cerebral vessel constriction in association with SAH from ruptured intracranial aneurysms as reported by Robertson (24) in 1949, cerebral vasospasm has been demonstrated frequently in both clinical and experimental situations. Subsequently, with extensive investigation of subarachnoid hemorrhage, attempts have been made to correlate cerebral vasospasm with the observed decreases in CBF and also with morbidity and mortality of this disorder.

It is very tempting to attribute the increases in CVR and associated decreases in rCBF seen in our investigations to cerebral vasospasm. In both clinical and experimental situations, a case has been made both for and against a correlation between cerebral vasospasm and reduced CBF. A positive correlation has been found in patients with SAH from ruptured intracranial aneurysms by many investigators (56,57,61,82,88,92,93). These observers, in general, have shown that the reduction in CBF results from narrowing of cerebral blood vessels demonstrated at angiography. The more severe the vasospasm, the greater the reduction in flow. Fergusson et al (57) reported, using a spasm grading system of mild, moderate, severe, that marked CBF reduction was present with severe vasospasm. However, with less severe spasm, there were no consistent blood flow changes.

Okawara et al (87) and Kak et al (86,90) found that cerebral vasospasm correlated with prolonged circulation time. Wilkins (65) has shown that abnormalities on brain scans of patients following SAH generally correlated well with the distribution of cerebral arterial spasm.

Conversely, other clinical investigators did not find any correlation between cerebral blood flow reduction and vasospasm following SAH (59,61,62,88). Zingesser et al (61) found reduced CBF even in patients without spasm, and in others with spasm CBF was normal. Heilbrun et al (59) reported a global reduction of CBF in their series of post-SAH patients. They discounted any relationship to vasospasm because spasm was always localized in their studies. Bergvall et al (62) found a poor correlation between CBF and cerebral vasospasm; decreased CBF was seen during the first few post-SAH days, at a time when spasm had not yet reached its peak. Furthermore, in some cases there was a reduction of CBF in the absence of spasm, and normal CBF in its presence. Bergvall et al (62) do qualify their results by suggesting that CBF could be affected by a marked reduction in the caliber of the conductance vessels. Mathew et al (88) state that cerebral vasospasm following SAH in patients does play a role in CBF reduction, but it is not the most important cause. They demonstrated relief of vasospasm with intracarotid phenoxybenzamine without any concomitant effect on cerebral blood flow. Grubb et al (55) conclude that the significance of cerebral vasospasm is unclear, but that it probably sets the stage for further events that cause CBF reduction. Kelly et al (60) using dynamic radioisotope brain scanning, found that reduced perfusion was present in patients with severe spasm; in those patients with less severe spasm perfusion was often normal. Kelly et al (60) also reported that perfusion could be reduced in the absence of vasospasm.

In experimental studies, spasm following induced SAH has not, in general, been demonstrated to correlate with the ensuing decrease in CBF (66,67,70,74), unless there was severe vasospasm (>50% reduction of original vessel diameter) (76). Following an induced SAH in dogs, Sugiura (97) found a biphasic vasospasm response that was associated with a biphasic reduction of CBF. Fraser et al (79), using carbon black injections, studied the perfusion deficit subsequent to induced SAH in monkeys. In general, there was poor correlation between cerebral vasospasm and perfusion defects. However, in those animals in which spasm did correlate with perfusion abnormalities it was suggested that 2 possible mechanisms existed. These are: (i) severe constriction of the conductance vessels transforming them into resistance vessels, or (ii) propagation of spasm from the larger vessels to the smaller resistance vessels. Asano et al (96), using a similar technique in dogs, demonstrated severe perfusion defects directly dependent upon the duration of ICP elevation. They postulated that cerebral vasospasm did have a role to play in decreased perfusion, but the major factor was disturbance of the microcirculation.

Following SAH in baboons, Hashi et al (100) observed a decrease in CBF in association with increased CVR, 24-48 hours post-insult. They attributed this increase in CVR to cerebrovascular spasm and perivascular edema of the smaller resistance vessels demonstrated at E.M. examination. Fein (99) found CVR increased and CBF decreased 3-4 hours post-SAH in monkeys. He postulated that the increased CVR was due to vasospasm, but the angiographic data was not presented.

It appears to be generally accepted that reductions in CBF do correlate with cerebral vasospasm when the degree of spasm is severe. The involvement of microcirculatory disturbances, not seen on cerebral angiography has also been demonstrated in association with CBF changes.

Varying degrees of cerebrovascular narrowing were present in all experimental animals of our 4 SAH volume groups at the first post-SAH angiographic examination. Both generalized and diffuse spasm was observed but this was not different for any of the 4 groups. The artificial CSF group did not show any evidence of vasospasm at this time. Vessel caliber measurements (CA, MCA, IDICA (C1,C2 - supraclinoid internal carotid artery and the petrous portion of the internal carotid artery)) revealed no difference in the degree of narrowing in the 4 SAH volume groups.

IDICA caliber measurements at this first angiographic examination demonstrated a significant decrease in diameter for all 4 SAH volume groups, but no change for the artificial CSF group. The reduction in caliber was no different for the 4 SAH volume groups.

At the second and final angiographic examination all 4 groups showed an improvement in the visually observed vasospasm; and subsequently verified by vessel caliber measurements. It was found that the recovery of spasm (from IDICA caliber measurements) was more complete in the 2 lower SAH volume groups. Again, the artificial CSF group did not exhibit any vasospasm, either visually or on diameter measurement. These findings have also been verified by E.M. examination of the cerebral vessels. Greater degrees of spasm were noted in the larger SAH volume groups while vasospasm was absent in the artificial CSF group. It should be noted, however, that the larger SAH volume groups vessels were prepared for E.M. examination just prior to death, whereas those of the lower SAH volume groups were prepared following a 20 hour survival period. It is possible that cerebral vasospasm may have undergone more attenuation during this period. E.M. study of cerebral vessels prepared at the same post-insult time for the various SAH volume groups was not performed. However, preparation of the cerebral vessels for E.M. study in the lower SAH volume groups, and in the artificial CSF group was carried out at the same post-insult time. It was found that varying degrees of spasm were present in the lower SAH volume group vessels compared with normal cerebral vessels in the artificial CSF group.

We also noted at these angiographic examinations that the proximal pericallosal artery (CA) in some animals showed a disproportionately greater degree of narrowing than did the surrounding vessels; no particular SAH group demonstrated this phenomena. A possible explanation of this finding is the proximity of this particular vessel to the jet of blood exiting from the needle placed in the chiasmatic cistern through which the SAH was induced. Another interesting feature in our study was the post-insult development of spasm in the cervical internal carotid artery in 80% of the experimental animals in the 2 larger SAH volume groups, and in 40% of those in the lower SAH volume groups.

At the first angiographic examination, the calculated CVR was shown to be elevated in each of the 1.0, 1.67 and 2.0 ml/kg SAH groups. Despite some recovery of spasm at the second angiographic examination CVR in the 1.0 and 1.67 ml/kg groups remained elevated at previous levels.

Our results indicate that the development of vasospasm is related to the injection of blood into the subarachnoid space, and not just to ICP elevation or volume of injection (no vasospasm was present in the artificial CSF group). Furthermore, post-insult vasospasm was greater for the larger SAH volume groups later in the experiment. Thus, the development of vasospasm appears to be due to the effects of the combination of blood, and of the volume injected into the subarachnoid space.

We have shown, in the larger SAH volume groups, that both rCBF reduction and degree of vasospasm were greater, and despite some recovery of the diameter of the cerebral vessels, rCBF remained persistently low and CVR elevated.

In 3 of the 4 animals dying acutely vasospasm was not different from surviving animals; the fourth animal did demonstrate more severe vasospasm. All of these "acute death" animals exhibited a more marked CVR elevation and a greater rCBF reduction compared with the survivors in the same groups. Only 1 of the 4 showed a larger decrease in CPP than the survivors. As previously discussed, the marked CPP decrease in this particular animal was due to the measurements being performed during cardiovascular decompensation just prior to death.

Our results are in agreement with Sundt et al (337) (in patients) and Symon et al (338) (experimentally) in that a reduction in CBF below a critical level of approximately 18 ml/100gm/minute is not recoverable, and is followed by deterioration and death. This phenomenon was seen in the animals dying acutely in our studies. Reduction in CBF, to levels above this "critical" level can be tolerated as long as the duration of the reduction is not excessive (131).

From our findings we postulate that cerebral vasospasm is, in part, associated with increased CVR and decreased rCBF, but it do does not play a major role. We believe that the major cause of CVR and subsequent rCBF disturbances lies at the microvasculature level. Petruk (66) and others (77,96,100), suggest the microvasculature as the major area responsible for CBF aberrations following SAH.

In general, support for the involvement of the microvasculature in post-SAH increased CVR and decreased CBF has been the experimental demonstration that the smaller resistance vessels have a role in the effects subsequent to SAH. Anatomical examination has shown that the small penetrating vessels are surrounded by a true extension of the subarachnoid space (339), making them available to the various vasoactive substances present in the subarachnoid space following SAH.

Several investigators (340,341) have demonstrated the presence of adrenergic fibres in association with both small pial arteries and even penetrating arterioles as small as 10-15 microns in diameter. The involvement of the sympathetic nervous system in the production of cerebral vasospasm has been postulated, but the subject is still under investigation. Fraser et al (342) and Peerless et al (341) have demonstrated a depletion of catecholamines in the perivascular plexuses on cerebral vessels following SAH, indicating functional sympathetic denervation of the cerebral arteries (336). Sympathectomy is associated with increased end-organ adrenergic sensitivity, resulting from the inability of the adrenergic nerve granulated vesicles to take up circulating catecholamines, which in turn terminate their effects on the receptor sites (343). In addition, following SAH, there is an increase in extraneuronal catecholamines (344) as well as circulating blood catecholamines (269,270) which appears to be related to the development of vasospasm (269). Thus, the denervation sensitivity post-hemorrhage may be in part, at least, responsible for the reduced CBF and increased CVR. The presence of adrenergic innervation of the penetrating cerebral vessels indicates the possibility of these mechanisms operating at the resistance level.

There is also the possibility that angiographically demonstrated vasospasm may propagate to the smaller resistance vessels by myogenic (79) or neurogenic mechanisms.

In association with these possible changes in the smaller vessels giving rise to decreased flow, subsequent ischemia will result in microvascular pathological changes that further compromise cerebral circulation. Hashi et al (77,100) in their experiments with SAH in baboons, demonstrated an increase in CVR and decrease in CBF 24-48 hours post-insult. E.M. studies revealed small vessel perivascular edema with swelling of astrocytes, which they felt to be involved in reducing CBF. Intracarotid phenoxybenzamine was effective in reducing CVR and increasing CBF. Intravenous 10% glycerol initially caused the same results. However, the effects of glycerol were only transient, and despite a decrease in ICP, CVR gradually rose and CBF fell. On the other hand, Mathew et al (88) found in patients with SAH that intracarotid phenoxybenzamine improved vasospasm, but not CBF, whereas intravenous 10% glycerol was effective in improving CBF. These authors suggest factors other than cerebral vasospasm to be responsible for CBF reduction (such as cerebral edema).

Fraser et al (79) demonstrated a poor correlation between cerebral vasospasm and angiography, and perfusion defects with carbon black following SAH in monkeys. They suggested that the smaller resistance vessels may be involved in the ischemic lesions. Asano et al (96) found, following SAH in dogs and perfusion with carbon black, non-filling of the fine cerebral capillary networks with sparing of the larger penetrating arterioles. The accompanying changes were intraparenchymal vascular bed narrowing due to astroglial, neuronal and endothelial swelling with intravascular aggregation of red cells. Asano et al (96) also demonstrated that the degree of non-filling and obliteration of the intraparenchymal capillary networks was more severe in the animals that experienced persistent ICP elevation and CBF reduction.

Similarly, following middle cerebral artery occlusion in monkeys, Crowell et al (126) showed that impairment of microvascular filling was directly related to the duration of the occlusion. These subsequent changes would then result in increased CVR.

Asano et al (96) reported that if ~~the~~ ICP fell to near normal levels, the deranged capillary systems recovered, and CBF returned to normal. These results are similar to our own in that we found a longer duration of ICP elevation in the larger SAH volume groups which was associated with larger increases in CVR and greater decreases in CBF. These groups did not experience the degree of recovery in these parameters seen in the lower volume SAH groups with shorter duration of increased ICP.

This disturbance of microcirculation following ischemia has been previously documented, and has been termed the "no-reflow" phenomenon (NRP) by Ames et al (124). They reported this phenomenon using a rabbit ischemic model (124). Similar microvascular changes have been demonstrated by Waltz et al (345) following middle cerebral arterial occlusion in cats and monkeys. Other investigators using ischemic, as well as SAH models have found endothelial and perivascular glial cell swellings to the degree of narrowing and obliteration of the capillary lumen (127) in association with sludging, hemoconcentration and small vessel stasis (123,129,345). Recently, Kim et al (346) have demonstrated this "no-reflow" phenomenon in dogs with artificially elevated ICP. In association with this, they found morphological changes in both the erythrocytes and platelets, and suggested that these changes may contribute to the disturbance of microcirculation in cerebral ischemia.

From our results, and from the investigations cited, it appears that microvascular abnormalities do play a significant and major role in post-SAH increased CVR and reduced CBF. Cerebral vasospasm, depending on the severity, is involved, but the major culprit appears to be the cerebral microvascular system.

TREATMENT WITH SODIUM NITROPRUSSIDE AND PHENYLEPHRINE

Morbidity and mortality following SAH have been attributed to the associated reduction in CBF. Cerebral vasospasm has been implicated as a factor in reducing CBF, but this mechanism is not definitely confirmed. As was discussed in the previous section our results, as well as those of others, showed CVR increase in association with CBF decrease following SAH.

In an attempt to improve post-SAH CBF and survival, various treatment regimes have been investigated. Recent reviews (43,131,132) discuss the many treatments under study. Most of these treatments involve the use of vasodilator drugs to improve the cerebral circulation, following the theory that angiographic cerebral vasospasm as well as smaller vessel spasm are involved with the CBF reduction. Other therapies include hypertensive agents and volume expanders (133,178(a),347) used for the treatment of postoperative neurological deterioration and cerebral vasospasm.

Recently, Allen (169) reported success with the treatment combination of intravenous phenylephrine and sodium nitroprusside in improving post-aneurysm surgery vasospasm and poor neurological condition in 2 of 3 patients with SAH.

Phenylephrine is a sympathomimetic amine with almost pure alpha activity (348). It is a vasoconstrictor of most vascular beds including pulmonary, renal, splanchnic and peripheral vessels. Phenylephrine almost completely lacks both chronotropic and inotropic cardiac actions. Following its administration, peripheral vascular resistance increases, followed by arterial hypertension and reflex bradycardia. In vitro, phenylephrine has been found to be relatively inefficient in contracting the cerebral vessels of both humans and experimental animals (168,349,350). In vivo, it does not have any effect on the cerebral vasculature (351). Chikovani et al (352) found that CBF was unaffected by phenylephrine administration in dogs under halothane anesthesia. These investigations demonstrated that phenylephrine does not disturb either the cerebral vasculature or CBF.

Sodium nitroprusside is a ferrous, hydrated pentacyano-compound, which was discovered by Playfair in 1849 (353). It is a potent direct vasodilator (354,355,356,357), whose vascular smooth muscle relaxation properties do not depend on alpha adrenolytic or beta sympathomimetic actions (354), and are unrelated to autonomic innervation

(170,356,358,359). At present, it is believed that sodium nitroprusside relaxant effects result from its action on excitation-contraction coupling by interfering with both the influx and the intracellular activation of calcium (354). Sodium nitroprusside induces hypotension because of its vasodilator property. The blood pressure has been found to return to normal within 5 minutes of the cessation of the drug (170,355,357,358,360).

In vitro, sodium nitroprusside has been shown to relieve vasospasm due to blood, serotonin and norepinephrine (168,170). It has also been effective in relieving cerebral vasospasm in vivo due to SAH both experimentally (170,177) and clinically (169). Because of its vasodilator properties and usefulness in relieving spasm, sodium nitroprusside may be effective in improving post-SAH CBF and survival.

In this, our second major investigation, we have studied the effectiveness of treatment with simultaneous intravenous sodium nitroprusside and phenylephrine in improving cerebral vasospasm, CVR, CBF and survival following induced SAH and SDH in monkeys. The effects of the treatment regime alone in the normal monkey have also been investigated. The experimental protocol of this study is similar to that of the SAH volume and artificial CSF series as described in Chapter II (Methods).

Stability of the experimental preparations in this treatment series was demonstrated by the constancy of the various physiologic measurements during the first 4 flow determinations.

The pathophysiological responses following the insult for the SAHRx and SDHRx groups were similar to those occurring in the 1.67 ml/kg SAH group. Immediately following the insult (CBF (5), there was a significant decrease in rCBF, which was associated with decreases in CPP (significant in the SAHRx group). As was the case in the 1.67 ml/kg SAH group, these changes demonstrated disturbed autoregulation following the hemorrhage. CVR was also found to be significantly elevated above resting levels in these 2 treated groups. Thus, the post-insult rCBF reductions were associated with both a failure of autoregulation and a CVR increase. Those experimental animals not receiving a hemorrhage experienced a minimal decrease in rCBF at this time; CPP was normal and CVR slightly increased. The CVR increase was significantly above resting levels but as described in Chapter III (Results), this increase in mean CVR and decrease in mean rCBF were due to minimal reduction of rCBF in 2 of the 3 animals. Nevertheless, the increase i CVR and decrease in rCBF of the SAHRx and SDHRx groups were significantly greater than these changes in the Rx alone group.

Following the insult, PaCO2 was significantly lower than normal in the 2 treated groups. As is well known, the relationship between PaCO2 and CBF is disturbed following

SAH (66,93,328). It is possible that low PaCO2 values, least in part, may be responsible for the reduction in BF seen post-SAH. In this study, following correction for ow PaCO2, we found that rCBF continued to remain reduced. he effects of low PaCO2 were minimal, and the rCBF reductions seen were mainly a direct result of the intracranial insult. We have already shown in the previous study that rCBF s low despite minimal or no change in PaCO2 in the lower volume SAH groups. Furthermore, in the larger volume H groups, rCBF remained reduced despite a return to normal of PaCO2. Thus, in our studies, PaCO2 changes played only a small part in post-SAH CBF reduction, with the major contributor being the intracranial insult.

Thus, the pathophysiological responses to the insult in the SAHRx and SDHRx groups, seen at the first post-hemorrhage CBF determination, are similar to those that occurred in the 1.67 ml/kg SAH group. Because of these similarities in the results for the 3 groups, we believe that we can directly compare the effects of treatment on the 2 insult treated groups with the results of the untreated group (1.67 ml/kg SAH).

Treatment with intravenous sodium nitroprusside and phenylephrine was instituted at the completion of BF (5). Sodium nitroprusside was administered first, and as adjusted until a MaBP decrease of at least 10-20 mmHg was obtained. The dosage was kept within the range described by

Allen (169), Brown et al (175) and Heros et al (170). Following an appropriate reduction in MaBP, phenylephrine was started. We attempted to elevate the MaBP to pre-insult levels with this drug but, in general, we were unable to do so, even though phenylephrine dosages 2-3 times those used by Allen (169) were employed. We did not continue to increase the phenylephrine level beyond this point, because of the possibility of renal vasoconstriction with subsequent ischemia. Furthermore, sodium nitroprusside has been found to have only a weak vasodilatory effect on the renal vasculature, and does not provide adequate protection to the kidney against renal ischemia associated with arterial hypotension (361). We were thus concerned that further increases in phenylephrine would result in renal vasoconstriction, and this, with the effects of sodium nitroprusside, despite any possible increases in blood pressure, would lead to renal ischemia and failure. Soon after the completion of the experiments, all surviving animals in the treatment study urinated, demonstrating that renal function was maintained during the treatment regime.

During the experimental studies the dosages of both sodium nitroprusside and phenylephrine were adjusted to maintain a stable MaBP.

CPP levels during the treatment regime for all 3 treatment groups remained lower than resting levels. This finding was significant in the SAHRx group for all CBF determinations, and in the other 2 groups for several of the CBF measurements. The etiology of the demonstrated decrease in CPP was a combination of decreased MaBP and elevated ICP. rCBF remained significantly lower than normal and CVR remained elevated in both the SAHRx and SDHRx groups. The slight improvements noted in rCBF and CVR following CBF (5) were felt not to be the result of the treatment, but rather to be due to the progression of the insult itself since similar changes were observed in the untreated 1.67 ml/kg SAH group. Towards the end of the experiments, CVR in the SDHRx group gradually returned to normal, despite a persistent decrease in rCBF. In the Rx alone group there was a persistent decrease (albeit slight) in rCBF during the treatment; CVR in this group was normal.

Cerebral angiography following the insult was performed after CBF (6), at a time when the treatment was already in progress. As was observed in the 1.67 ml/kg SAH group, generalized and diffuse vasospasm was present in both the SAHRx and SDHRx groups. Similar degrees of visually observed cerebral vasospasm were present in all experiment animals of these 3 experimental groups. IDICA caliber measurements revealed a significant decrease in vessel diameter for the 2 treated groups a finding similar to that for the 1.67 ml/kg SAH group.

The second post-insult cerebral angiographic examination for the SAHRx and SDHRx groups was performed during the treatment regime and some improvement in vasospasm was seen but IDICA caliber measurements remained smaller than normal (significant for the SAHRx group). There was no difference in the degree of vasospasm, either observed or measured, between the SAHRx and 1.67 ml/kg SAH groups.

The third angiographic examination, performed after the therapy was discontinued demonstrated further improvement in spasm but IDICA diameters were still smaller than pre-insult values.

No cerebral vasospasm or vasodilation were demonstrated in the Rx alone group at angiographic examinations, during, or following the treatment.

On cessation of the treatment regime, CPP recovery was noted in the SAHRx and SDHRx groups; to levels slightly below and slightly above normal respectively. CPP in the Rx alone group showed a slight improvement, but remained lower than normal. These improvements in CPP resulted from a recovery towards resting levels for both MaBP and ICP.

In the SAHRx and SDHRx groups, rCBF remained significantly lower than normal following the cessation of treatment; that of the Rx alone group fell to below the resting levels.

CVR in all 3 treatment groups at this final CBF determination (CBF (11)) was elevated above normal levels (significant for the SAHRx group).

From our results, it is apparent that the treatment combination of intravenous sodium nitroprusside and phenylephrine was not effective in improving post-hemorrhage cerebral vasospasm or rCBF.

The rCBF reduction in association with decreased CPP in the Rx alone group demonstrates that this treatment regime impairs autoregulation. The greatest decrease in CPP in this group during the studies was to a mean of 56 mmHg, which is above the accepted lower limit of autoregulation (35-40 mmHg) (102,108,118,122,243,324). Thus, since CPP levels in the Rx alone group were above this lower limit (and above 60 mmHg during most CBF determinations) we believe that the regime of phenylephrine and sodium nitroprusside impaired autoregulation in our series. Similarly, in the SAHRx and SDHRx groups, there were marked rCBF reductions associated with decreased CPP, demonstrating impaired autoregulation in these groups. It is well known that autoregulation is impaired following SAH (67,78,94,328,362). The impaired autoregulation found in the SDHRx group may have resulted from cerebral trauma due to the injection of blood in the subdural space, or from some subarachnoid blood, but may also have been caused by the treatment itself.

As reported at the beginning of this section, phenylephrine does not affect either the cerebral vasculature or CBF. Thus, it is most likely that sodium nitroprusside was the agent responsible for disturbed autoregulation, in the Rx alone group, and probably was, at least in part, responsible for the failure of autoregulation in the SAHRx and SDHRx groups.

Crockard et al (171), using rhesus monkeys, found a loss of autoregulation with the administration of sodium nitroprusside. Using this drug to cause 5-10%, 10-20% and 20-40% reductions in MaBP, they found that as MaBP was reduced, CBF fell in an essentially linear fashion. A 5% reduction in MaBP was associated with a 16.0±5.0% decrease in CBF. Ivankovich et al (363) reported that sodium nitroprusside, in doses too small to affect the peripheral circulation, and administered to the cerebral circulation in goats, resulted in CBF reductions which were directly related to the dose given. They also observed that, with recommended clinical dosage of intravenous sodium nitroprusside (3-8 ugm/kg/min), arterial hypotension occurred and CBF remained unchanged. This result was attributed to the cerebral vasodilatory effect of the drug. However, with a test dose of angiotension in the awake goat receiving intravenous nitroprusside, both MaBP and CBF rose concurrently. Angiotension given to awake goats not receiving sodium nitroprusside showed an increase in MaBP, but CBF remained constant. Ivankovich et al (363) concluded that sodium nitroprusside not only had a cerebral vasodilatory effect, but also impaired autoregulation. Other experimental investigations have also demonstrated the impairment of cerebral autoregulation with sodium nitroprusside (172,364,365). Brown et al (175) studied the effects of sodium nitroprusside on CBF in patients under investigation for various neurological disorders. Those patients suspected of having impaired autoregulation or cerebral vasospasm were excluded from the study. They reduced the MaBP in these patients by 10-33% with intravenous sodium nitroprusside in dosages 0.27-4.4 ugm/kg/min, and found a mean CBF reduction of 15.9±5.6%, which was significantly lower than normal thus demonstrating autoregulatory impairment due to this drug. These investigators suggested that sodium nitroprusside was not as effective in dilating the cerebral vessels as it was for the peripheral vasculature, with a resultant decrease in the amount at cardiac output to the cerebral circulation. Unfortunately, these authors did not report ICP, CPP or CVR in their studies; parameters that would be useful in the interpretation of their results.

Griffiths et al (176) reported on the results of the use of sodium nitroprusside in patients undergoing operative clipping of cerebral arterial aneurysms under general anesthesia. Of the 20 patients studied, 19 were clinical grade I and II, and 1 was grade III, using the Hunt and Hess system. A mean MaBP decrease to 67.2 mm Hg was found representing a 42% reduction. The duration of the drug infusion was 17-93 minutes, and the total amount given 3.5-16.0 mg. Their results, in general, demonstrated a decrease in CVR and preservation of grey matter CBF, indicating intact autoregulation. However, in patients who had elevated grey flow prior to the sodium nitroprusside, a decrease in CBF was noted following the drug administration. It was postulated by these authors that the cerebral vasculature in these patients was already maximally dilated, resulting in grey matter CBF passively following the blood pressure (disturbed autoregulation).

Stoyka et al (366) showed in dogs, anesthetized with thiopentone and ketamine, that autoregulation remained intact to decreased arterial blood pressure following administration of sodium nitroprusside. With a reduction of CPP to 60 mm Hg, there was 8% decrease in CBF. However, further decreases to 30 mm Hg were associated with steadily decreasing CVR, maintaining CBF at a stable level.

Akerman et al (177) found in baboons anesthetized with phenoperidine, droperidol and ketamine, that 7-10 ugm/kg/min of sodium nitroprusside infusion was associated with a stable CBF and a decreased CVR. Doses higher than this level resulted in decreasing CVR and elevation in CBF. Both of these parameters returned to resting levels on cessation of the drug. With further dosage increase to 50-80 ugm/kg/min similar results were obtained, but on completion of the therapy, 3 of 5 animals demonstrated steadily increasing CBF values, and 2 showed decreasing CVR. Sodium nitroprusside administered in doses of 80-300 ugm/kg/min caused CBF increases and the animals died from severe irreversible hypotension. These investigators concluded that autoregulation was maintained until MaBP tell to about 50 mm Hg, with the dose range 6-10 ugm/kg/min of sodium nitroprusside. Higher doses were accompanied by erratic CBF responses and death of the experimental animal.

Investigations using sodium nitroprusside in laboratory animals, and in patients with minor cerebral disorders, have shown that this drug, in general, does not improve cerebral circulation. Furthermore, many studies, including our own, indicate that sodium nitroprusside impairs cerebral autoregulation.

Akerman et al (177), as a continuation of their experimental studies in baboons, reported that cisterna magna injection of both blood and serotonin resulted in cerebral vasospasm, increased CVR and decreased CBF. Administration of sodium nitroprusside in dosages 8-19 ugm/kg/min was associated with a decrease in arterial blood pressure, reduced CVR, significant CBF increase and relief of cerebral vasospasm. Our results do not support these findings. We found a persistent reduction in CBF and increase in CVR following both SAH and SDH, with no improvement in cerebral vasospasm.

These conflicting results might be explained by the major differences between the 2 experimental models. Akerman et al did not use phenylephrine as a part of the therapy, and CBF calculation was made using the stochastic (H/A) method, however these differences are unlikely to cause the marked differences in the results obtained in the 2 studies. The dose of sodium nitroprusside in our series was 2-4 times less than the lowest mean dosage in their work, and the duration of therapy in our investigation was twice as long as theirs. The SAH was induced in Akerman's study by the injection of 1-2 ml of blood into the cisterna magna of the baboon, whereas we used 1.67 ml/kg of body weight into the chiasmatic cistern of the monkey. They did not report the type of blood or whether it was heparinized or not. MaBP reduction in Akerman's study following the insult was similar to that obtained in our studies, but CBF reduction and CVR elevation were markedly less dramatic than observed in our expermental preparation. Akerman demonstrated a CBF decrease of only 5 ml/100gm/min representing only 12.5% of resting value. In our model, mean CBF reduction was 33 ml/100gm/min in both the 1.67 ml/kg SAH group and SAHRx group, and 27 ml/100gm/min in the SDHRx group, representing 60%, 56% and 56% respectively of the control values. Similarly, they documented a CVR increase of only 0.4 CVR units following the hemorrhage, whereas we found CVR increases of greater than 1.0 units. It is our belief that differences in the degree of insult and its associated effects between the 2 experimental models explain the conflicting results. We contend that our model (exhibiting a more tramatic insult, greater decreases in CBF and increases in CVR) more closely approximates the situation occurring clinically, and that sodium nitroprusside (with phenylephrine) is inadequate in improving post-insult CBF and does impair autoregulation.

Heros et al (170), following cisterna magna injection of 2.0 ml of fresh autogenous blood at a rate of 0.4 ml/min in the dog, found an acute reduction in the basilar artery caliber to a mean of 68±4% (SEM) of pre-insult value. With intravenous sodium nitroprusside using a mean dose of 3.0 ugm/kg/min they demonstrated, within 15 minutes, an increase in diameter to 96±4% (SEM) of normal. On cessation of the drug, spasm returned within 30 minutes to the pre-drug degree. Angiographic examination during infusion of the drug was performed anywhere from 30-90 minutes after the hemorrhage. Our observations revealed that the initial vasospasm, following the insult in the untreated 1.67 ml/kg SAH group showed some improvement at 75 minutes post-insult. The treatment was not effective in improving cerebral vessel caliber beyond that occurring spontaneously with time. Kuwayama et al (367) using the same model as Heros et al (170), demonstrated that "within the first few hours" of the SAH, the basilar artery caliber improved spontaneously to more than 70% of control. In these studies, 3 of 9 animals, after 90 minutes, had recovered vessel caliber to within 80-90% of control. We observed spontaneous recovery of IDICA diameter to 80±4% of control in the untreated 1.67 ml/kg SAH group by approximately 173 minutes post-insult. Heros et al

(170) reported that sodium nitroprusside was effective in improving post-SAH vasospasm to a degree greater than would have occurred spontaneously. Differences between their experimental model and ours include their use of a smaller SAH volume and induction rate, as well as a species difference; drug dosages were similar. These factors may be responsible for the discrepancies between the results for the 2 series. Heros' group did not measure CBF, nor did they correlate the neurological conditions of the experimental animals with vasospasm.

Allen (169) has used the treatment combination of sodium intropr ussi de (2.5-5.5 ugm/kg/min) and phenylephrine (0.30-0.38 ugm/kg/min) intravenously in 3 postoperative aneurysm patients that demonstrated increasing neurological deterioration with associated cerebral vasospasm. With this treatment, he reported improvement in the clinical condition and a concurrent recovery of vasospasm. One of the patients developed cerebral infarction and did not improve with the treatment program. However, close inspection of the cerebral angiograms presented in his paper reveals that the reported "dramatic" increase in diameter of the large cerebral vessels was not as marked as he had indicated. Improvement in vessel caliber of some vessels was demonstrated, but others remained unchanged or were even reduced. The distal cerebral vessels, especially in case 2 of his series, do not show alleviation of spasm. CBF measurements were not performed. As previously discussed in Chapter I

(Introduction), clinical status is directly related to CBF, and for a reduction in CBF to occur, vessel caliber of the large cerebral vessels must be reduced by more than 50% of the original diameter. The alleviation of spasm reported in Allen's series, under these conditions, does not appear to be solely responsible for the improvement in neurological status; spontaneous recovery of these patients remains a possibility. As Allen admits, the series is small, the correlation of clinical improvement and observed spasm alleviation is inconclusive, and further investigation into the effectiveness of sodium nitroprusside and phenylephrine as a treatment regime is needed.

We observed that ICP became elevated in the treatment series (SAHRx, SDHRx and Rx alone) following institution of the treatment program, and remained so far the duration of the treatment. In general, during this same post-insult time period in the untreated SAH groups, no increase in ICP was found. On cessation of the treatment, ICP declined, but did not return completely to resting levels in the SDHRx and Rx alone groups. Unfortunately, of the investigations involved with the relation of sodium nitroprusside and cerebrovascular hemodynamincs, only several of them reported ICP changes. As in our studies, Akerman et al (177) also report an ICP elevation with sodium nitroprusside that recovered an cessation at the drug. They also report CBF increase and CVR decrease with this drug; this would, in part, explain the increase in ICP. On the other hand, in our investigation, ICP was elevated when CBF remained low and CVR high. Brown et al (172), using nitroprusside in rhesus monkeys, did not show any change in ICP or CVR with this drug. Other investigators (364,368,369,370) have reported ICP elevation, in patients and experimental animals, following sodium nitroprusside administration. Tobaddor et al (370),in cats, showed that after 10-15 minutes of elevated ICP, it spontaneously returned to normal despite continuation of nitroprusside. Candia et al (364) demonstrated, using cynomolgus monkeys, that following an initial rise in ICP, it returned to an intermediate level within 3 minutes. The increase was postulated to result from CVR reduction, and increased cerebral blood volume due to the cerebral vasodilatory effects of the drug. These authors consider the use of sodium nitroprusside hazardous in states of already elevated ICP.

ICP increases found in our treatment studies most likely resulted from some cerebral vasodilatory effect of sodium nitroprusside. This effect was not seen at cerebral angiography, and thus must have occurred at the smaller non-visualized vessel level. However, although this relationship may be possible, the overall effects of this drug in our model were not effective in improving post-insult CBF. Instead, it impaired autoregulation and was directly responsible for the CBF decrease in the treated animals not subjected to a hemorrhage (Rx alone group).

In the SAHRx group, 2 animals died acutely. The mean neurological grade of this group at 5 hours was 4, and at 20 hours all animals were dead. These survival results are similar to those of the untreated 1.67 ml/kg SAH group. As was the case with the acutely dying animals in the 1.67 ml/kg SAH group, those animals dying acutely in the SAHRx group had post-SAH rCBF levels that remained low in the range 14-18 ml/100gm/min. These flow values are in the region of the "critical" flow level, as discussed previously in this chapter. In these animals, rCBF remained low, without recovery, until death.

Similarly, those animals dying acutely demonstrated greater increases in CVR following the SAH than was seen in the survivors. ICP changes for the acutely dying animals were no different from those of the remaining animals in the SAHRx group. All of the experimental animals, except for 1, had similar post-insult CPP levels. The exception was 1 animal that showed a persistently low CPP throughout the complete experiment.

As was found in the 1.67 ml/kg SAH group, the acutely dying animals in the SAHRx group did not demonstrate more severe vasospasm than did the surviving animals.

Thus, it appears that those animals in the SAHRx and 1.67 ml/kg SAH groups that died acutely (within 5 hours of the insult) behaved similarly during their post-SAH deterioration. It was also shown that those experimental animals surviving the 5 hour observation period in these 2 groups were of similar poor neurological status at the first neurological examination and were all dead by 20 hours post-insult. Therefore, our results demonstrate that the treatment regime of sodium nitroprusside and phenylephrine is totally ineffective in improving post-SAH rCBF, CVR, vasospasm, morbidity and mortality.

The SDHRx group in general presented a neurological status of grade 2 in both observation periods, similar to the behaviour of the untreated SDH animals. Again, the treatment regime is shown to be ineffective.

Three animals in the Rx alone group were grade 2 after 5 hours. Two were dead at 20 hours and 1 was sacrified at approximately 10 hours, at a point where there was marked deterioration and when death appeared imminent. These time periods are taken in relation to the timing of the insult in the other treatment groups. The poor outcome of those animals receiving only the treatment regime and not undergoing an intracranial insult raised doubts as to the safety of this treatment regime in cynomolgus monkeys. However, the animals in the SDHRx group survived both the insult and the treatment regime. The experimental animals of the Rx alone group were in no physiological difficulty during the 5 hour observation period, and the cause of death in all 3 cases could not be attributed to either the experimental design or procedure, aside from possible adverse effects of the treatment regime.

Toxic and lethal effects of sodium nitroprusside in both patients and experimental animals have been reported in the literature. Jack (371) reported the death of a previously healthy patient following general anesthesia of thiopentone, suxamethonium, nitrous oxide and halothane, during which sodium nitroprusside was administered to obtain hypotension. Resistance to the hypotensive effect of sodium nitroprusside was encountered, and larger than usual doses were given. Following the procedure, blood gas analysis demonstrated severe metabolic acidosis, hypocapnia and normoxemia. The patient subsequently developed respiratory arrest and died. MacRae and Owen (372) reported the development of metabolic acidosis in a patient undergoing stapedectomy with routine general anesthesia and sodium nitroprusside for its hypotensive effects. Similarly, resistance to nitroprusside hypotension was encountered, and the dose was increased. The patient's condition in the recovery room was poor, respiration was rapid, and investigations showed severe metabolic acidosis, normal PaO2 and hypocapnia in association with low standard bicarbonate. The acidosis was treated effectively with bicarbonate and the patient recovered. Pertuiset et al (373) have reported upon the deaths of 2 patients undergoing aneurysm surgery each of whom recieved greater than "recommended" dose of sodium nitroprusside because of physiologic resistance to its hypotensive effects.

Similar problems have been encountered experimentally, McDowell et al (374) using baboons anesthetized with phencyclidine, halothane and nitrous oxide, and mechanically ventilated, found that in 4 of these animals hypotension was easily attained with a mean dose of 1.25±0.22 mg/kg/hr and a total dose of 26.2±5.2 mg of sodium nitroprusside. On cessation of the drug, the blood pressure recovered and the animals remained stable. Four other baboons demonstrated resistance to the hypotensive effects of nitroprusside, and to obtain the required effects, the mean dose was 7.29±1.74 mg/kg/hr and the total dose 108.7±29.2 mg. In these experimental animals the blood pressure did not recover on cessation of the drug. Investigations showed the presence of metabolic acidosis as well as acidotic CSF, resulting from documented lactic acidosis and anaerobic metabolism. CMRO2 calculations in these animals demonstrated poor oxygen utilization. These baboons fared poorly. On the other hand, the first group of 4 baboons that showed blood pressure recovery were found to have only mild degrees of systemic metabolic and CSF acidosis and they did well.

The common features of these clinical and experimental observations are resistance to the hypotensive effects of sodium nitroprusside, increased dosage and subsequent metabolic acidosis.

Sodium nitroprusside [$Na_2[Fe(CN)_5(NO)].2H_2O$], in vivo is initially metabolized non-enzymatically by its inteaction with sulfhydral groups in red blood cells and other tissues, with release of cyanide radicals (355,375). Cyanide is detoxified by enzymatic linkage to sulfydral groups forming thiocyanate by the hepatic enzyme rhodanese (transsulfurase) (376). Thiocyanate is removed almost exclusively by the kidney, with a normal half-life of approximately 1 week (377). If there is a build up of thiocyanate, it is oxidized back to cyanide by thiocyanate oxidase found in red blood cells (378).

Cyanide is a well known poison that disrupts cellular respiration by combining with cytochrome oxidase forming a cytochrome oxidase-cyanide complex. Cytochrome oxidase plays an important role in cellular utilization of oxygen, and when inactivated by combination with cyanide, cytotoxic hypoxia results leading to cellular dysfunction and death (379). Cytotoxic hypoxia refers to cellular hypoxia in the presence of a normal blood oxygen content. With disruption of the normal aerobic processes, anaerobic metablism occurs, resulting in metabolic acidosis. Levine et al (380) have shown that following cyanide administration to rats, neuronal necrosis occurs. They felt this to result from cyanide inhibition of cytochrome oxidase in the central nervous system with ensuing celluar hypoxia, which in turn gives rise to tissue and CSF acidosis.

It is probable that the systemic metabolic and CSF acidosis reported in clinical and experimental studies result from these metabolic changes. In the previously reported investigations, blood lactate, cyanide and thiocyanate levels were not documented, and only McDowall et al (374) reported lactate levels in CSF with sodium nitroprusside. Nevertheless, these various investigators postulated that large doses of sodium nitroprusside resulted in metabolic acidosis from the effects of cyanide accumulation which was most likely responsible for the observed morbidity and mortality.

Our results demonstrate a progressive fall in PaCO2 for the 3 treated groups during sodium nitroprusside administration (significant for the SAHRx and SDHRx groups), with slight improvement following cessation of the drug. Small decreases in PaCO2 were found towards the completion of the experiments in the 1.67 ml/kg SAH group and the artificial CSF group, but not to the extent seen in the treated groups. All 3 groups in the treatment series showed increases in Vt and RR towards the end of the studies. This was not seen in the untreated series. The pH values for the treated groups were slightly greater than resting but remained within the accepted limits of normal. The association of hyperventilation and normal pH levels indicates metabolic acidosis with respiratory alkalosis compensation.

The animal in the Rx alone group that was sacrificed at 10 hours "post-hypothetical" insult showed severe metabolic acidosis that remained uncompensated despite marked hyperventilation. The remaining 2 animals in this group were dead at 20 hours. On cessation of the treatment regime, the arterial blood pressure of these animals did not recover. Similar findings have been reported by McDowall et al (374). It thus appears that the poor outcome for animals in the Rx alone group resulted from the toxic effects of sodium nitroprusside.

As documented in the Results section, the dosage of sodium nitroprusside, total dose and duration of treatment were similar for all 3 treatment groups. The dosage (ugm/kg/min) and total dose (ugm/kg) in our studies were factors of 5-10 less than those used by McDowall et al (374) in the baboons that showed recovery. Duration of therapy was similar in the 2 investigations. MacRae et al (372) demonstrated the development of metabolic acidosis in a patient with resistance to sodium nitroprusside, but receiving an amount far less than that given to "recovery" baboons in McDowall's study. They believed that patient response to the drug was unpredictable, but that adverse effects appeared to result in patients showing resistance to sodium nitroprusside. In our series, only 3 experimental animals, 1 in each treatment group demonstrated relative resistance to the hypotensive effects of sodium nitroprusside.

Thus, despite the fact that death of the 3 animals in the Rx alone group most likely resulted from the toxic effects of the drug, we have not been able to demonstrate an overdose of sodium nitroprusside, or resistance to its hypotensive effects.

Vitamin B12 (hydroxycobalamin) has been shown to be a potent cyanide antedote (381). Wilson et al (382) commented that patients with vitamin B12 deficiency from malnutrition or other disorders are more susceptible to the toxic effects of sodium nitroprusside. Caution should therefore be utilized when using nitroprusside in patients with vitamin B12 deficiency (383). The true state of nutrition of our monkeys was evaluated by general appearance, weight, hemoglobin concentration and physiological measurements. The 3 monkeys of the Rx alone group were from a different shipment of monkeys than those of the other treatment groups. Two of the 3 animals weighed less than the overall mean of the other groups. Hemoglobin concentration in these 2 was also lower than the accepted norm in the cynomolgus monkey. It is interesting that these 2 animals were those that failed to show recovery of arterial blood pressure following cessation of the treatment regime.

It is probable that the monkeys of the Rx alone group were of poor nutritional status with resultant deficiency in vitamin B12 as well as the cyanide detroxifying enzymes. I conclude, therefore, that the demise of these 3 animals most probably was due to the known toxic effects of sodium nitroprusside.

There has been no conclusive evidence that sodium nitroprusside alone, or in combination with phenylephrine is effective in improving post-SAH cerebral vasospasm, CVR, CBF and outcome. Our results demonstrate that the treatment regime of sodium nitroprusside and phenylephrine not only is ineffective, but also disturbs cerebral autoregulation, and that the toxicity of sodium nitroprusside is an ever present problem.

CONCLUSION

We have studied the pathophysiological responses to increasing volumes of subarachnoid blood in an attempt to determine some of the factors responsible for the high morbidity and mortality following SAH. Our investigations have shown that "poor outcome" subsequent to induced SAH results from decreased rCBF, respiratory centre dysfunction and poor oxygenation, either singly or in combination. Reduced rCBF following the insult was a consequence of elevated CVR and disrupted autoregulation. The etiology of increased CVR was in the main due to disturbances of the cerebral microcirculation. Cerebral vasospasm following the SAH was involved, but was shown not to play a major role in CVR changes. Respiratory centre dysfunction was demonstrated by the occurrence of apnea and hyperventilation following the insult; this condition was shown to result from ICP changes during and following the SAH. Abnormal blood oxygenation was occasioned by the development of physiologic pulmonary shunting and NPE subsequent to ICP elevation.

These factors, either singly or in combination, are at least in part responsible for a poor outcome following SAH. Other factors, such as cerebral metabolic changes subsequent to SAH, are most likely involved but were not investigated in the reported studies.

A possible mechanism by which the several noted factors are involved in the mortality of SAH(AR) is as follows:

respiratory centre dysfunction following SAH is known to occur (because of the subsequent respiratory pattern abnormalities). Furthermore, from previous work, including our own, death following SAH is initiated by respiratory arrest and then followed by cardiovascular decompensation. Thus, subsequent to SAH, if rCBF remains decreased and hypoxemia persistent, cerebral ischemia and hypoxia will result, adding insult onto injury of the respiratory centres with subsequent cessation of function and death.

Another possible mechanism for mortality following SAH is the development of persistent cerebral ischemia and hypoxia leading to cerebral edema, ICP elevation and cerebral compression. If not alleviated, these events will continue in cyclical fashion with subsequent decompensation of vital centres and death.

In the present work we also studied the effectiveness of the treatment combination of sodium nitroprusside and phenylephrine in improving post-SAH reduced rCBF, elevated CVR, cerebral vasospasm and survival. This treatment regime was found to be totally ineffective. In addition, we found that this drug combination not only disrupted cerebral autoregulation but was also lethal to some of our experimental animals. These adverse effects were most likely due solely to sodium nitroprusside.

In the clinical situation of SAH, definitive efforts should be made to reduce ICP, to improve cerebral perfusion and to maintain adequate oxygenation. For the reduction of ICP, hyperosmolar agents, barbiturates, hypocapnia and total body cooling should be instituted if indicated. The development of hydrocephalus following SAH should be carefully monitored and if present relieved by a shunting procedure. Reduction of ICP will improve cerebral perfusion. As described previously other modes of improving post-SAH cerebral blood flow have been attempted but at present a definite effectiveness of such efforts has not been demonstrated. Volume expansion in combination with arterial hypertension has been shown to be effective in improving reduced rCBF following experimentally induced SAH, as well as in patients with a deteriorated neurological condition post-aneurysm clipping. However, this form of therapy in the early period of patients with SAH(AR) could be hazardous.

Adequate oxygenation and tracheo-bronchial care in patients with SAH(AR) is mandatory. If pulmonary shunting and NPE are present, oxygen administration, mechanical ventilation and PEEP are the only means at present for combating the problem. However, with mechanical venilation and PEEP, one runs the risk of increasing ICP.

From these investigations, we have documented that sodium nitroprusside can be a dangerous drug. It continues to be used frequently in patients for its hypotensive effect, especially in neurosurgery. We suggest that when it is used, adequate assessment of the patient's nutritional status, renal and hepatic function and vitamin B12 levels be made. Special precautions, including observing for patient's resistance to its hypotensive effects, total dosage and rate of administration, should be taken during the administration of sodium nitroprusside.

For the future, further research needs to be insituted to unravel the etiology of elevated CVR and reduced CBF following SAH in an attempt to develop a therapeutic program to improve these parameters for better survival. Volume expansion and controlled hypertension, in association with antifibrinolytic agents, although hazardous, may yield good results in patients with recent SAH(AR) if used judiciously.

The mechanisms responsible for the development of NPE following SAH need to be elucidated, and treatment of this condition requires detailed study.

The present work has been directed towards the outstanding problems of morbidity and mortality following SAH(AR). The principal results of these investigations indicate the importance of ICP, CBF, respiratory pattern and oxygenation, either singly or in combination, in determining the outcome following SAH. It is to be reconciled that many other factors could also play strategic roles.

While answers to some of the questions initially posed have been found, others remain to be clarified. In fact, many more questions are now raised in the writer's mind concerning the phenomenon of SAH.

It is hoped that some of the questions both initially posed in this thesis as well as those that have arisen as a result will be investigated by future research workers.

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THE UNIVERSITY OF ALBERTA

PATHOPHYSIOLOGY AND TREATMENT OF SUBARACHNOID HEMORRHAGE IN THE CYNOMOLGUS MONKEY

by

© CHARLES SHELDON ROTHBERG

A THESIS
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IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
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19. Pre-Insult. MaBP, HR, ICP, CPP, rCBF, CVR and VC (vessel caliber) for the SAHRx, 1.67 ml/kg SAH and artificial CSF groups. 439

20. "Time to change", "time to peak" and "maximum change" for ICP, MaBP, R (respiratory pattern) and RVP for the SAHRx, 1.67 ml/kg SAH, SDHRx and artificial CSF groups subsequent to the insult. 440

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22. Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control) at CBF determinations 5 - 10 for the 1.67 ml/kg SAH and artificial CSF groups and 5 - 11 for the SAHRx. 442

23. Pre-Insult. Vt (tidal volume), RR (respiratory rate), PaCO2, PaO2, pH, RVP (right ventricular pressure) and A-aDO2 (alveolar-arterial oxygen difference) for the SAHRx, 1.67 ml/kg SAH and artificial CSF groups. 443

24. Pre-Insult. Vt, RR, PaCO2 and PaO2 as % of control, and pH, RVP and A-aDO2 for CBF determinations 5 - 10 for the 1.67 ml/kg SAH and artificial CSF groups, and 5 - 11 for the SAHRx group. 444

25. Pre-Insult. MaBP, HR, ICP, rCBF, CVR and VC (vessel caliber) for the SDHRx and SAHRx groups. 445

26. Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control) for CBF determinations 5 - 11. 446

27. Pre-Insult. Vt (tidal volume), RR (respiratory rate), PaCO2, PaO2, pH, RVP (right ventricular pressure) and A-aDO2 (alveolar-arterial oxygen difference) for the SDHRx and SAHRx groups. 447

28. Post-Insult. Vt, RR, PaCO2 and PaO2 as % of control, and pH, RVP and A-aDO2 for CBF determinations 5 - 11. 448

29. Pre-Insult. MaBP, HR, ICP, CPP, rCBF, CVR and VC (vessel caliber) for the Rx alone, SAHRx and SDHRx groups. 449

30. Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control) for CBF determinations 5 - 11. 450

31. Pre-Insult. Vt (tidal volume), RR (respiratory rate), PaCO2, PaO2, pH, RVP (right venticular pressure) and A-aDO2 (alveolar-arterial oxygen difference) for the Rx alone, SAHRx and SDHRx groups. 451

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32. Post-Insult. Vt, RR, PaCO2 and PaO2 as % of control, and pH, RVP and A-aDO2 for CBF determinations 5 - 11. 452

33. Neurological grade at 5 hours and 20 hours post-insult for the SAHRx, SDHRx, Rx alone, 1.67 ml/kg SAH and Artificial CSF groups. 453

34. Mean fresh brain weight, brain weight/body weight and formaldehyde brain weight gain for the SAHRx, SDHRx, Rx alone, 1.67 ml/kg SAH and artificial CSF groups. 454

35. Degree of vasoconstriction of cerebral vessels at E.M. for the SAHRx and Rx alone groups. 455

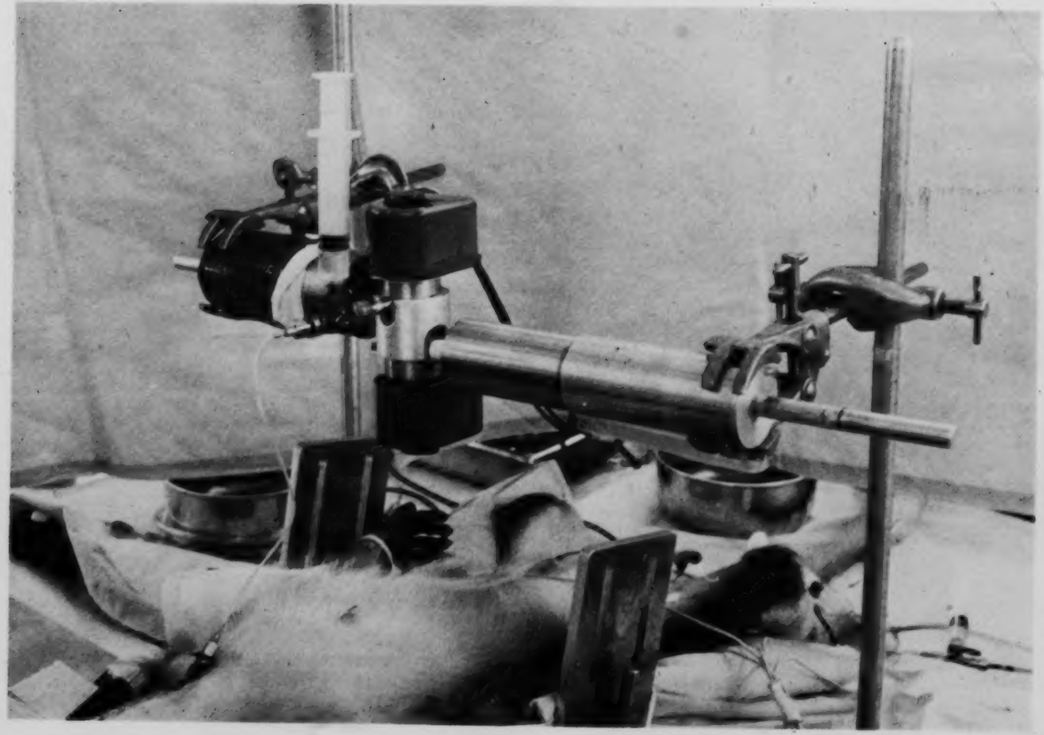


Figure 1: Automatic injector system.

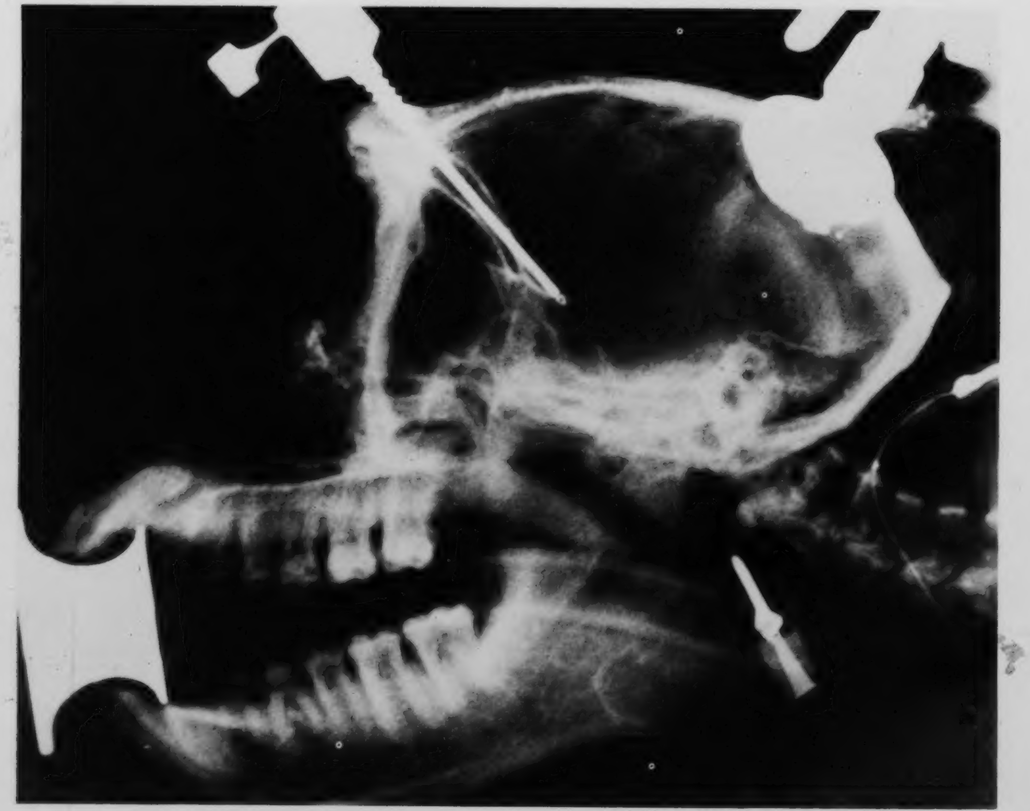


Figure 2: Lateral roentgenogram showing tip of injection needle with side holes in position in the chiasmatic cistern.

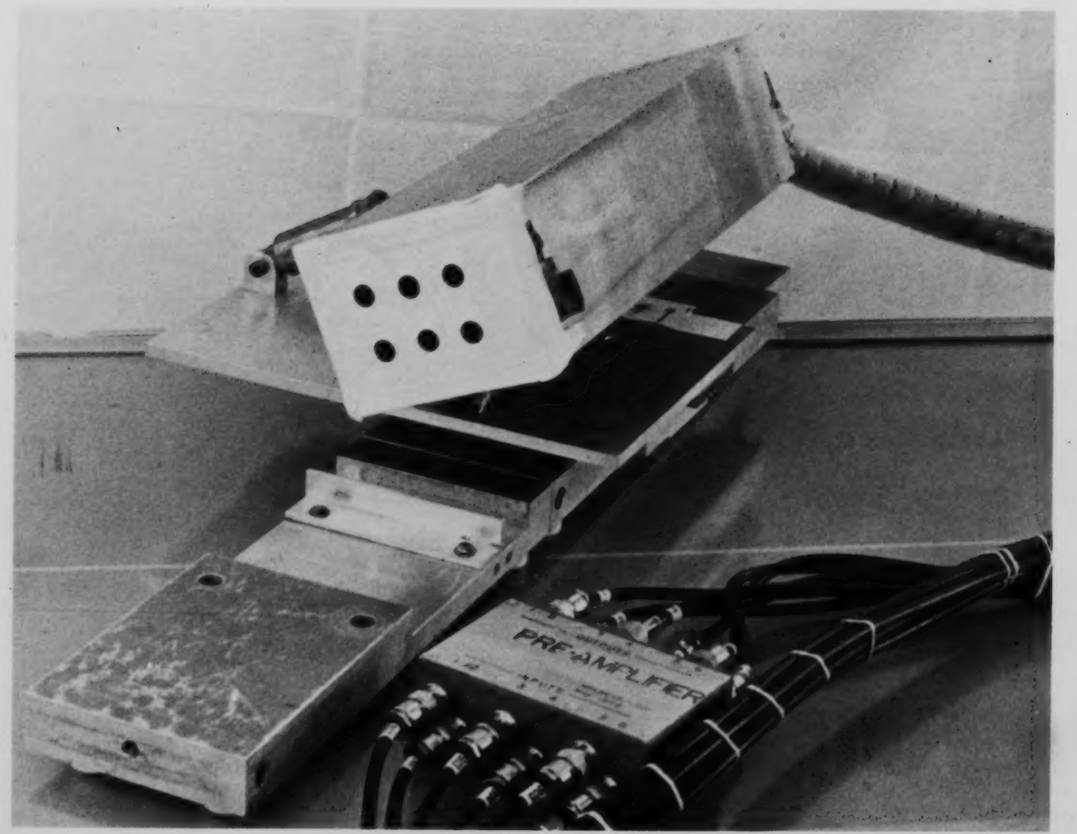

PRE-AMPLIFIER

Figure 3: Six detector scintillation counter system.

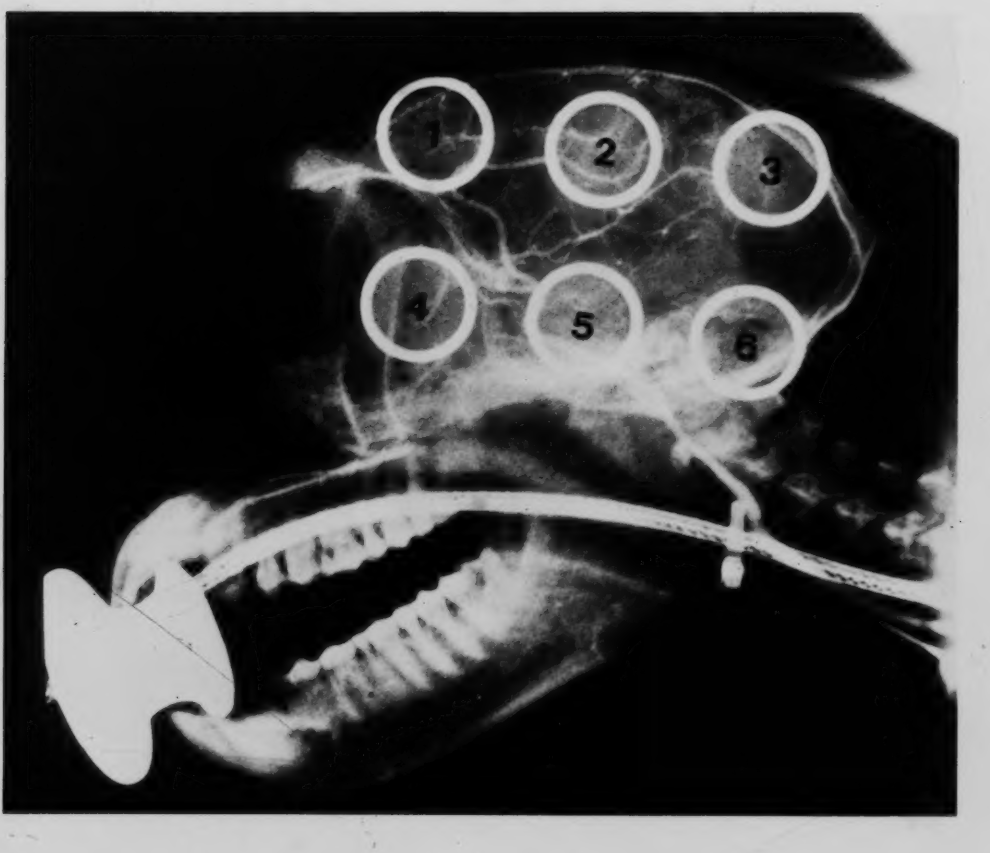


Figure 4: Lateral cerebral angiogram showing the relative positions of the 6 scintillation detectors.

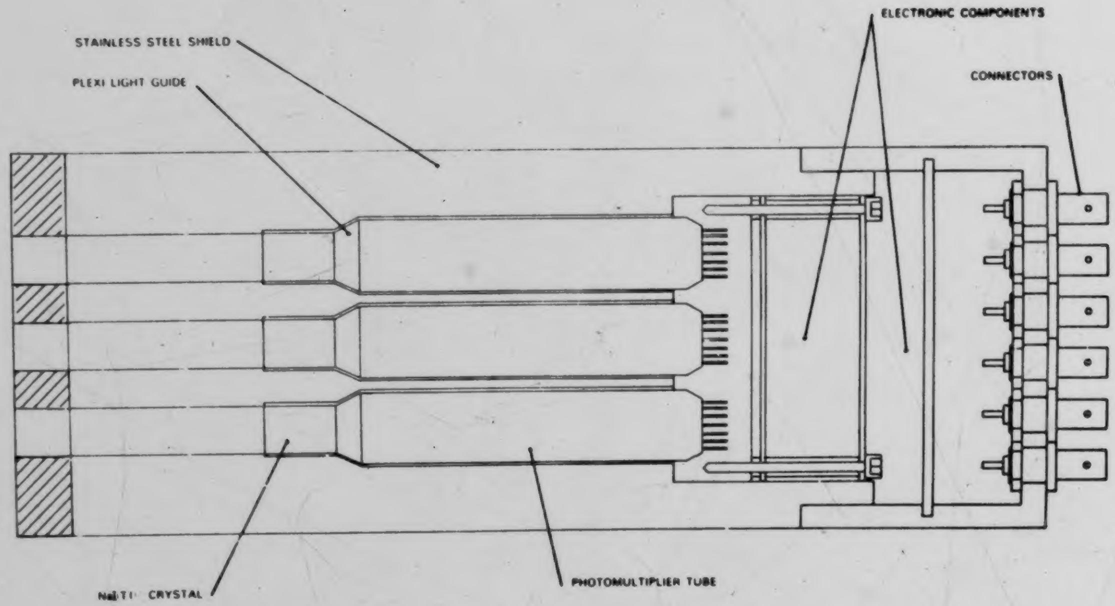

STAINLESS STEEL SHIELD
PLEXI LIGHT GUIDE
ELECTRONIC COMPONENTS
CONNECTORS
NaI(Tl) CRYSTAL
PHOTOMULTIPLIER TUBE

Figure 5: Multidetector system (superior view)

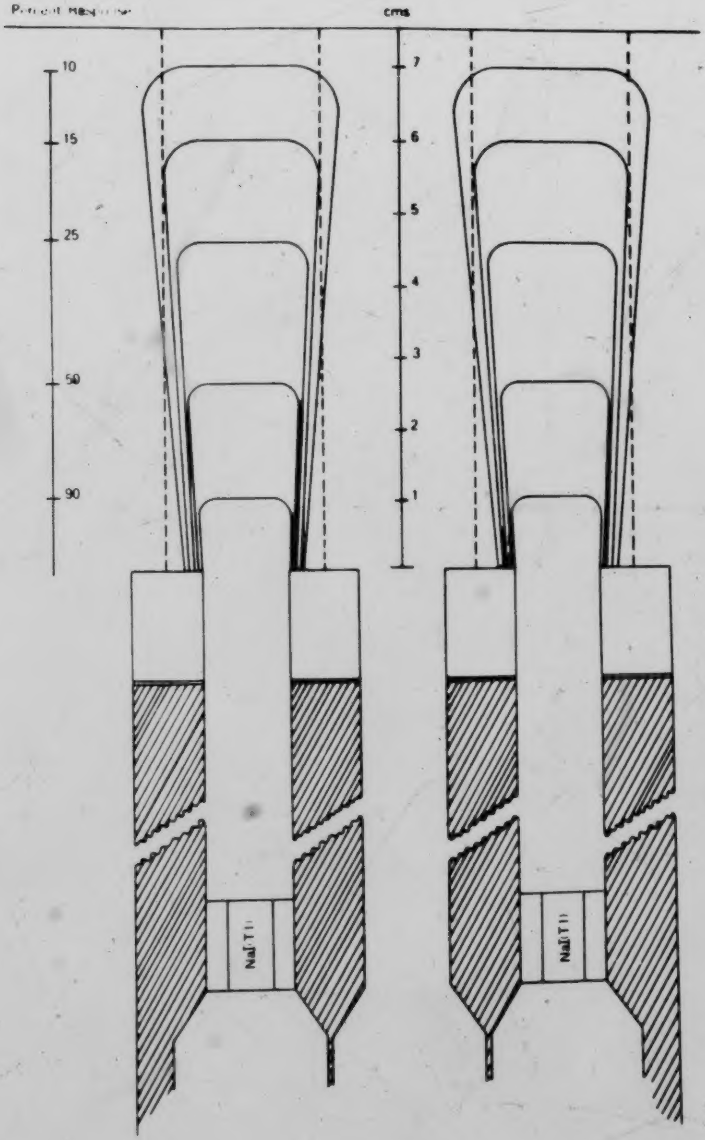

Percent Response
cms
10
15
25
50
90
7
6
5
4
3
2
1
NaI(Tl)
NaI(Tl)

Figure 6: Isoresponse curves for 2 adjacent collimated detectors with a point source of 133 Xenon in water. Isocount contour at the 90, 50, 25, 15 and 10% response levels.

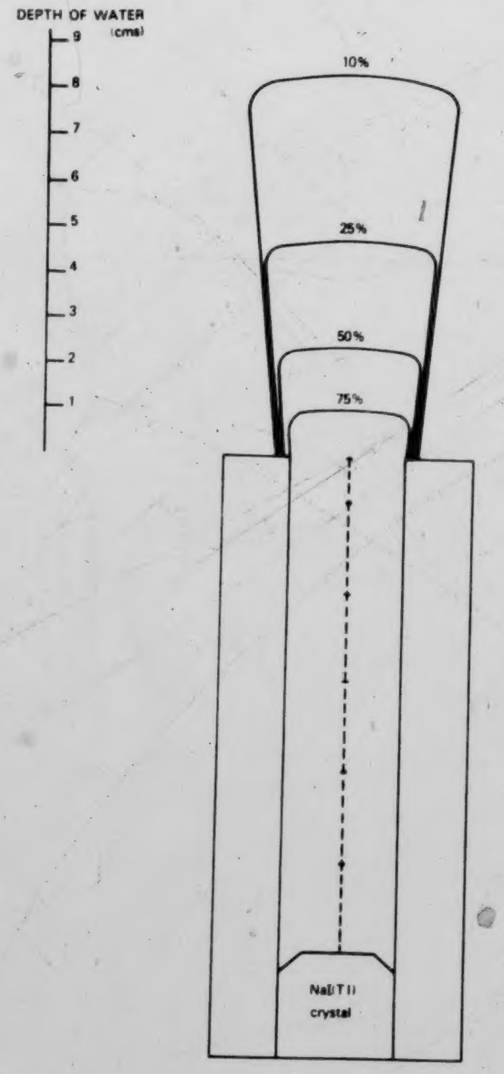

DEPTH OF WATER (cms)
9
8
7
6
5
4
3
2
1
10%
25%
50%
75%
NaI(Tl) crystal

Figure 7: Collimated isoresponse curves with a point source of 133 Xenon in water. Isocount contours at the 75, 50, 25 and 10% response levels.

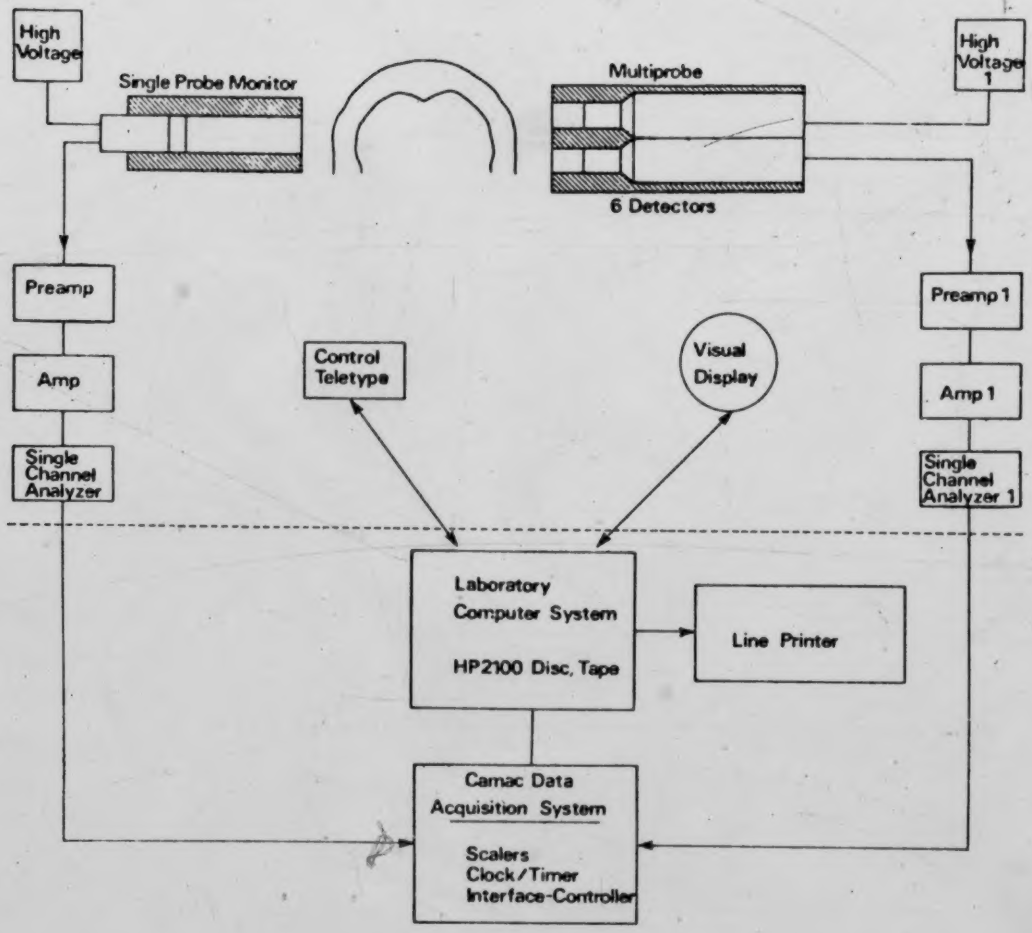

High Voltage
Single Probe Monitor
Multiprobe
High Voltage 1
6 Detectors
Preamp
Amp
Single Channel Analyzer
Control Teletype
Visual Display
Preamp 1
Amp 1
Single Channel Analyzer 1
Laboratory Computer System
HP2100 Disc, Tape
Line Printer
Camac Data Acquisition System
Scalers
Clock/Timer
Interface-Controller

Figure 8: Instrumentation for hemispheric and regional cerebral blood flow studies.

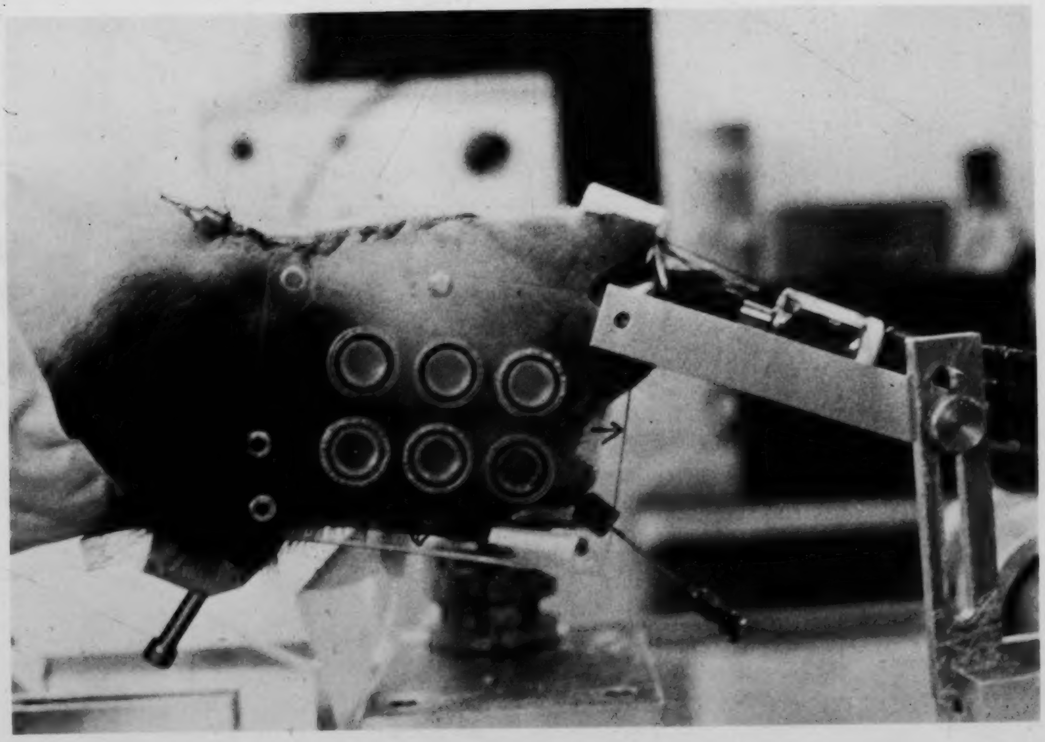


Figure 9; Positioning of monkey head relative to the template.

S

VESSEL MEASUREMENT LOCATION

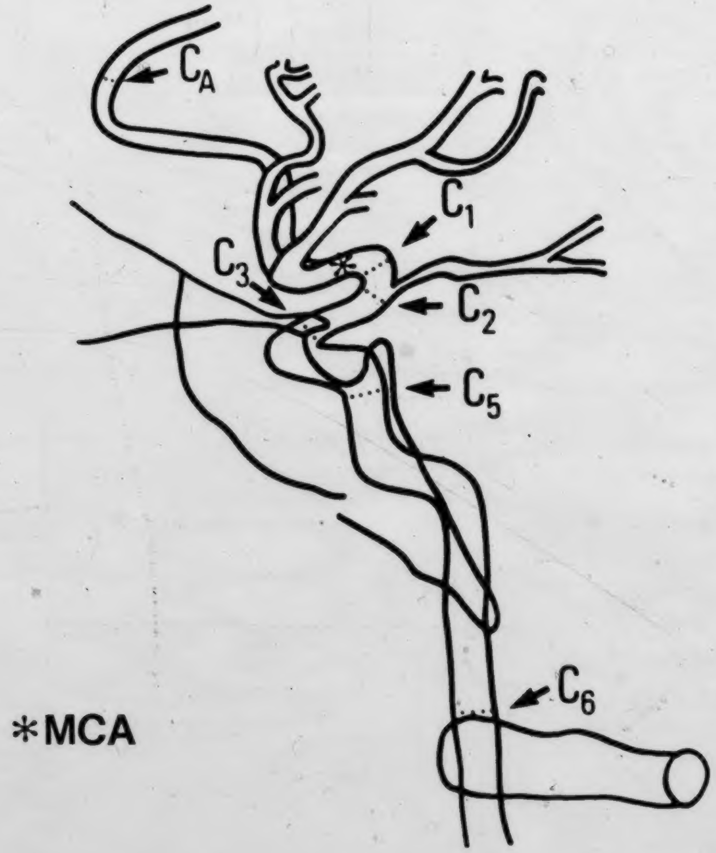


Figure 10: Schematic diagram showing sites of cerebral arterial caliber measurements.

C_A- proximal pericallosal artery; C_1-intradural internal carotid artery above the posterior communicating artery; C_2-intradural internal carotid artery below the posterior communicating artery; MCA- middle cerebral artery.

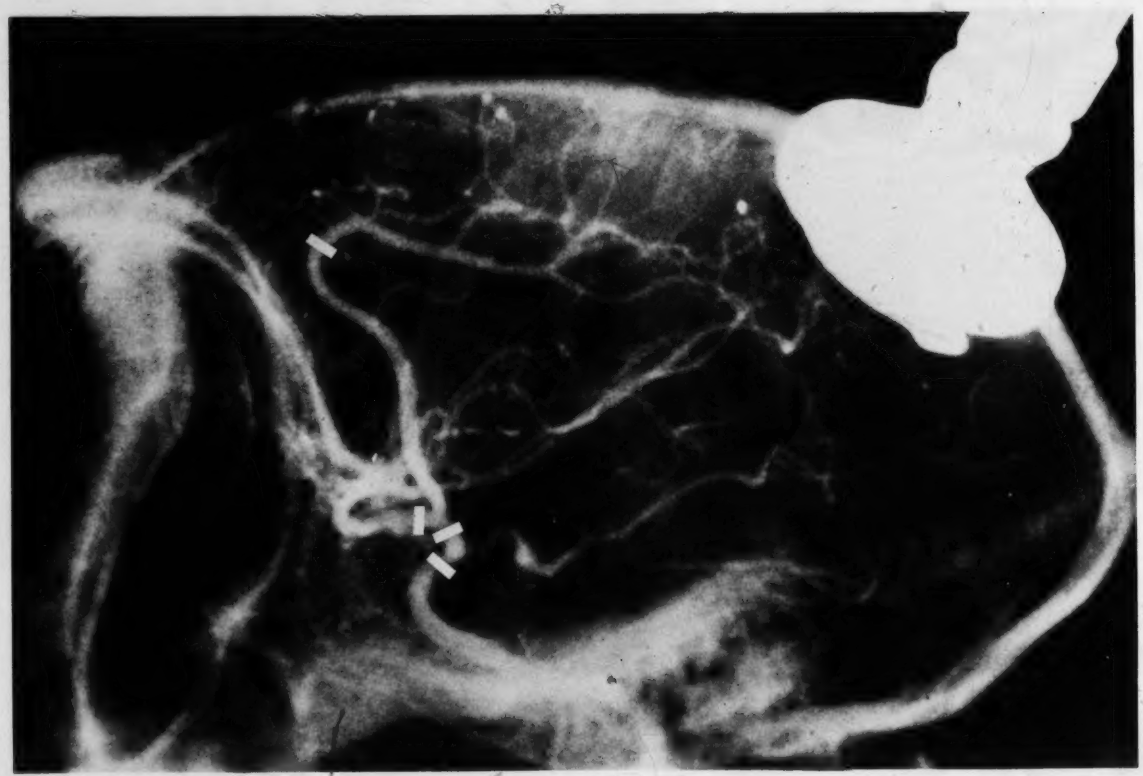


Figure 11: Lateral cerebral angiogram showing sites of cerebral arterial caliber measurements.

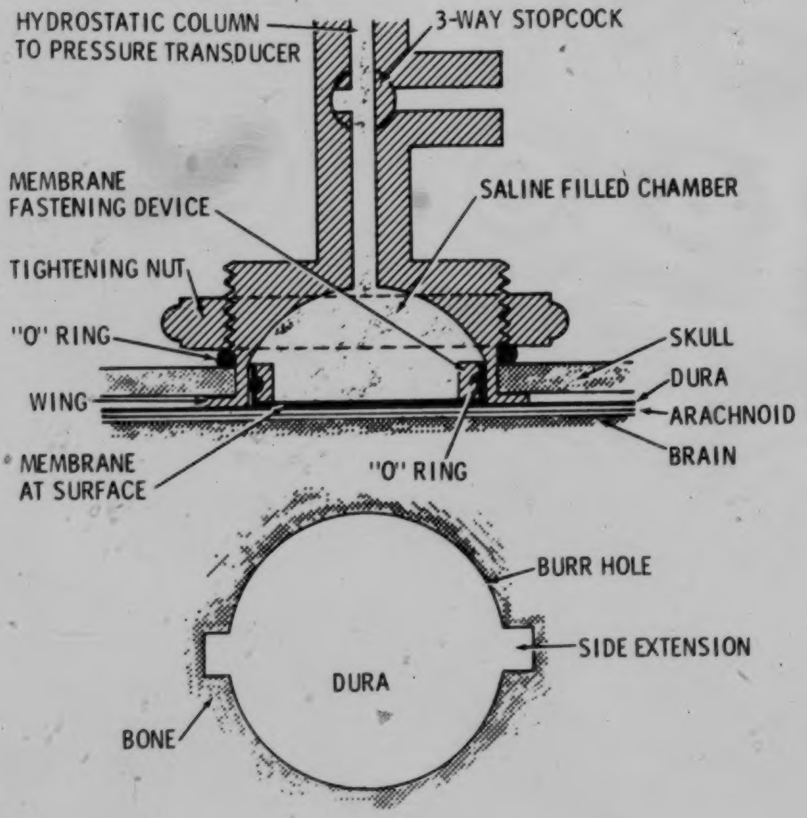

HYDROSTATIC COLUMN
TO PRESSURE TRANSDUCER
3-WAY STOPCOCK
MEMBRANE
FASTENING DEVICE
SALINE FILLED CHAMBER
TIGHTENING NUT
"O" RING
SKULL
DURA
WING
ARACHNOID
MEMBRANE
AT SURFACE
"O" RING
BRAIN
BURR HOLE
SIDE EXTENSION
DURA
BONE

Figure 12: Schematic diagram of the ICP measuring device and its positioning.

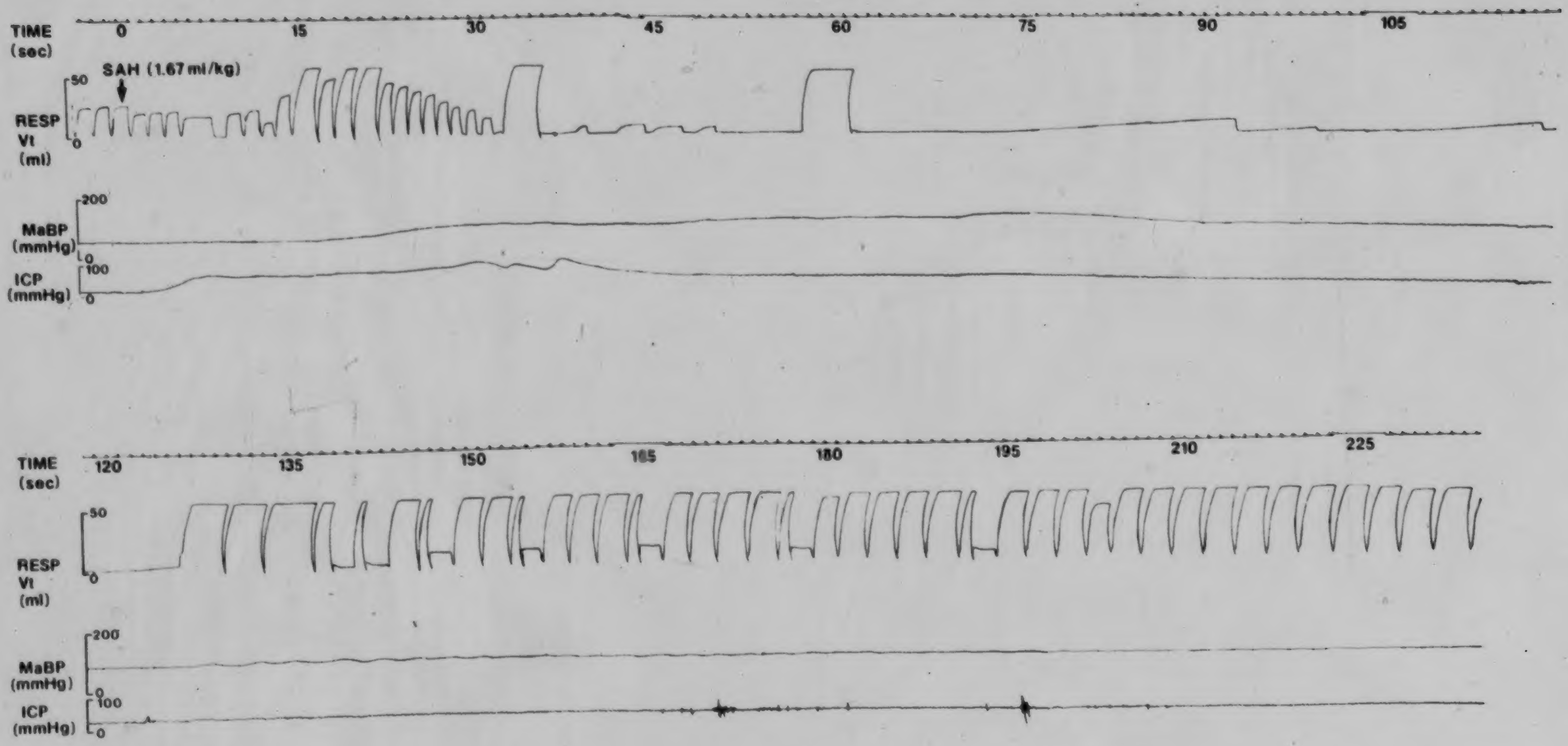


Figure 13: ICP, MaBP and respiratory resonses to an induced SAH.

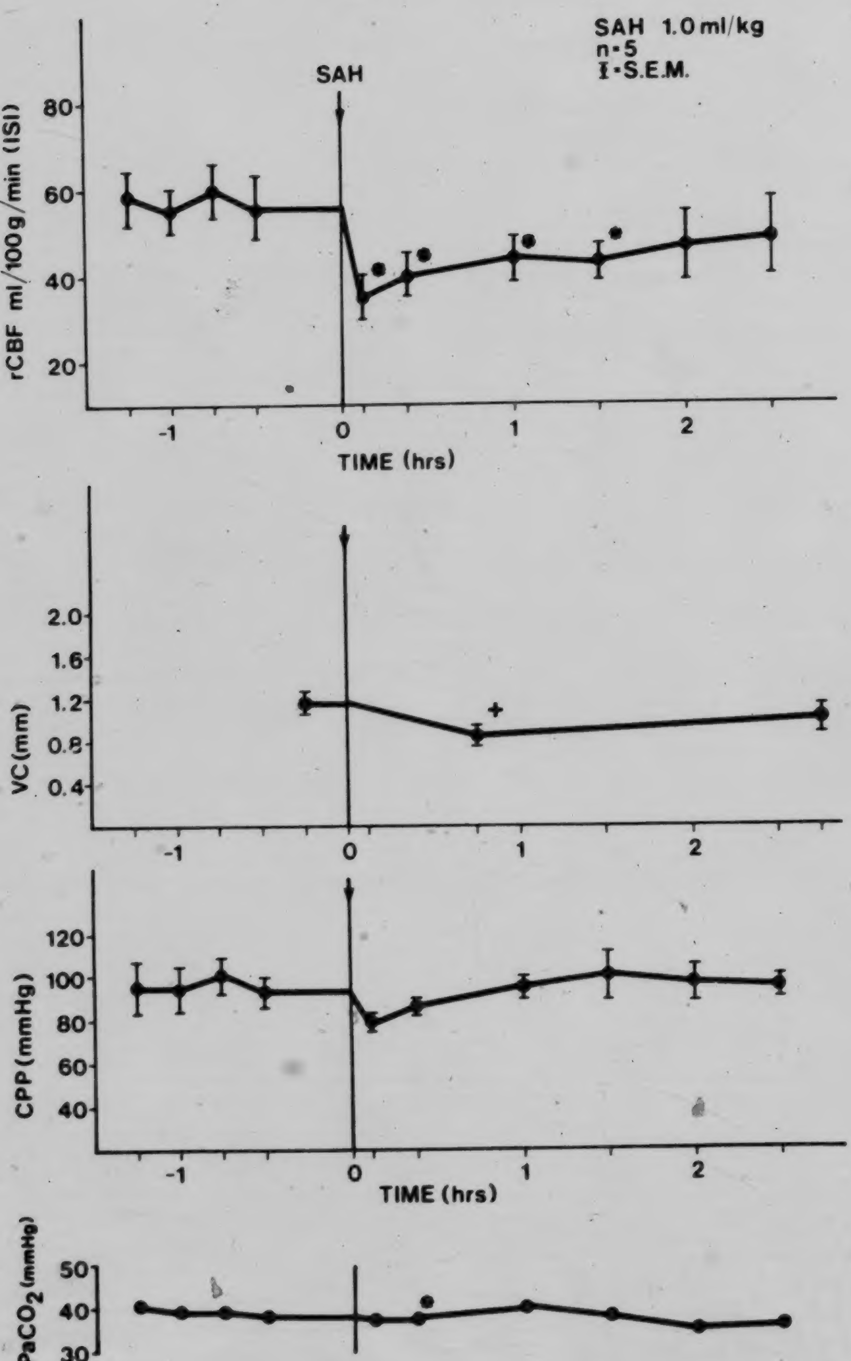


Figure 14: Pre and post-SAH rCBF, VC (vessel caliber), CPP and $PaCO_2$ for the 1.0 ml/kg SAH group.

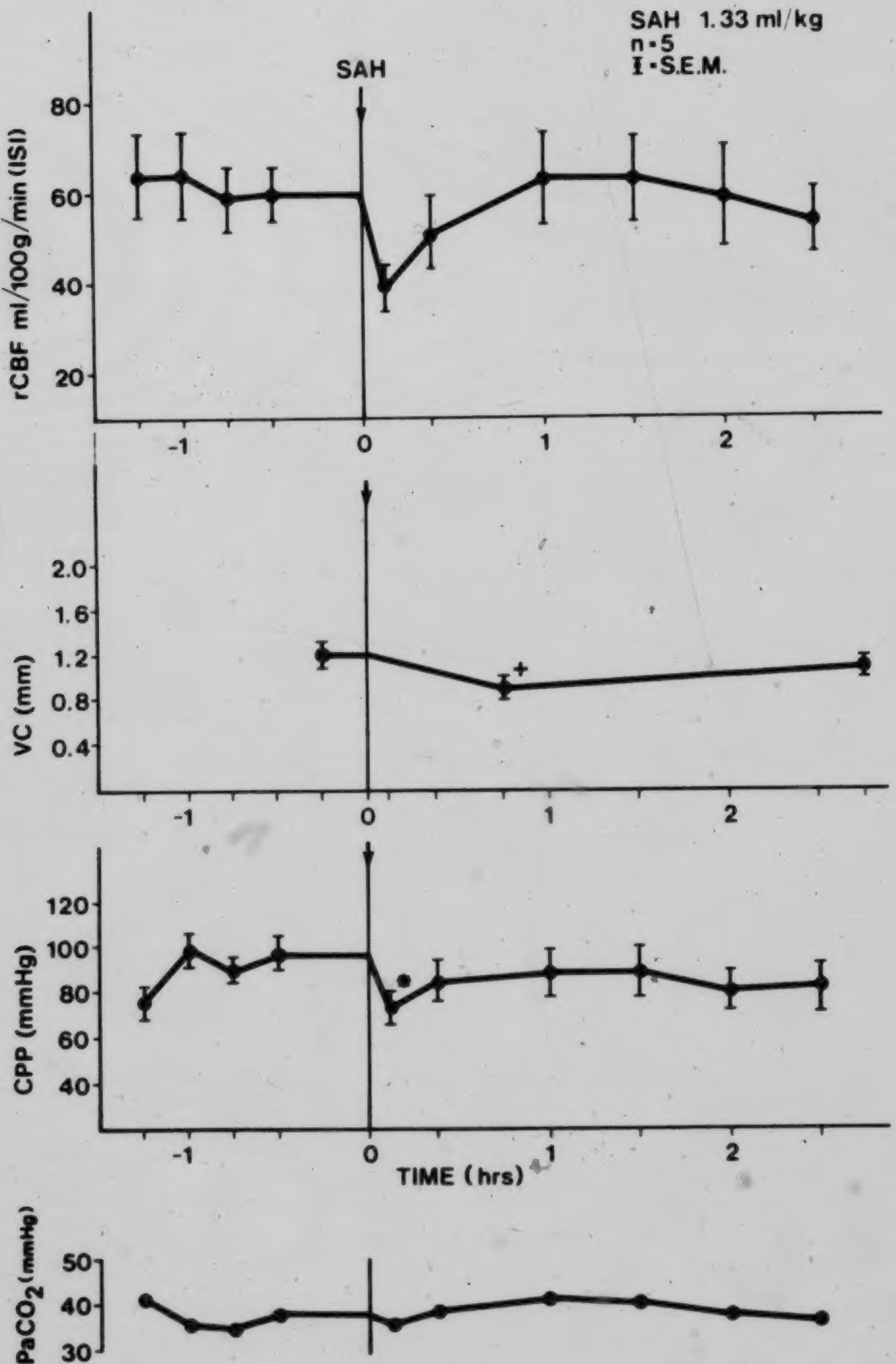


Figure 15: Pre and post-SAH rCBF, VC (vessel caliber) CPP and $PaCO_2$ for the 1.33 ml/kg SAH group.

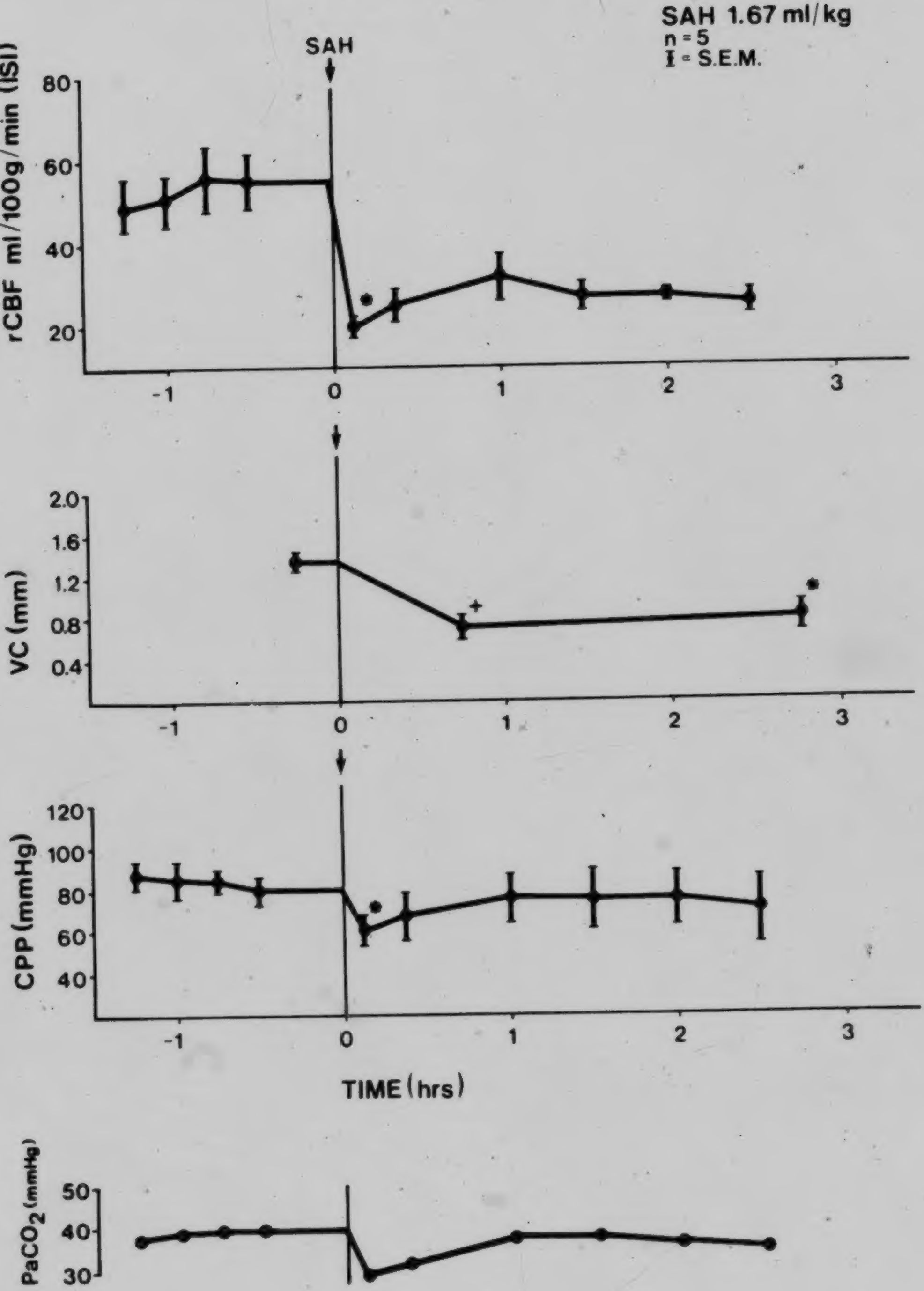


Figure 16: Pre and post-SAH rCBF, VC (vessel caliber), CPP and PaCO$_2$ for the 1.67 ml/kg SAH group.

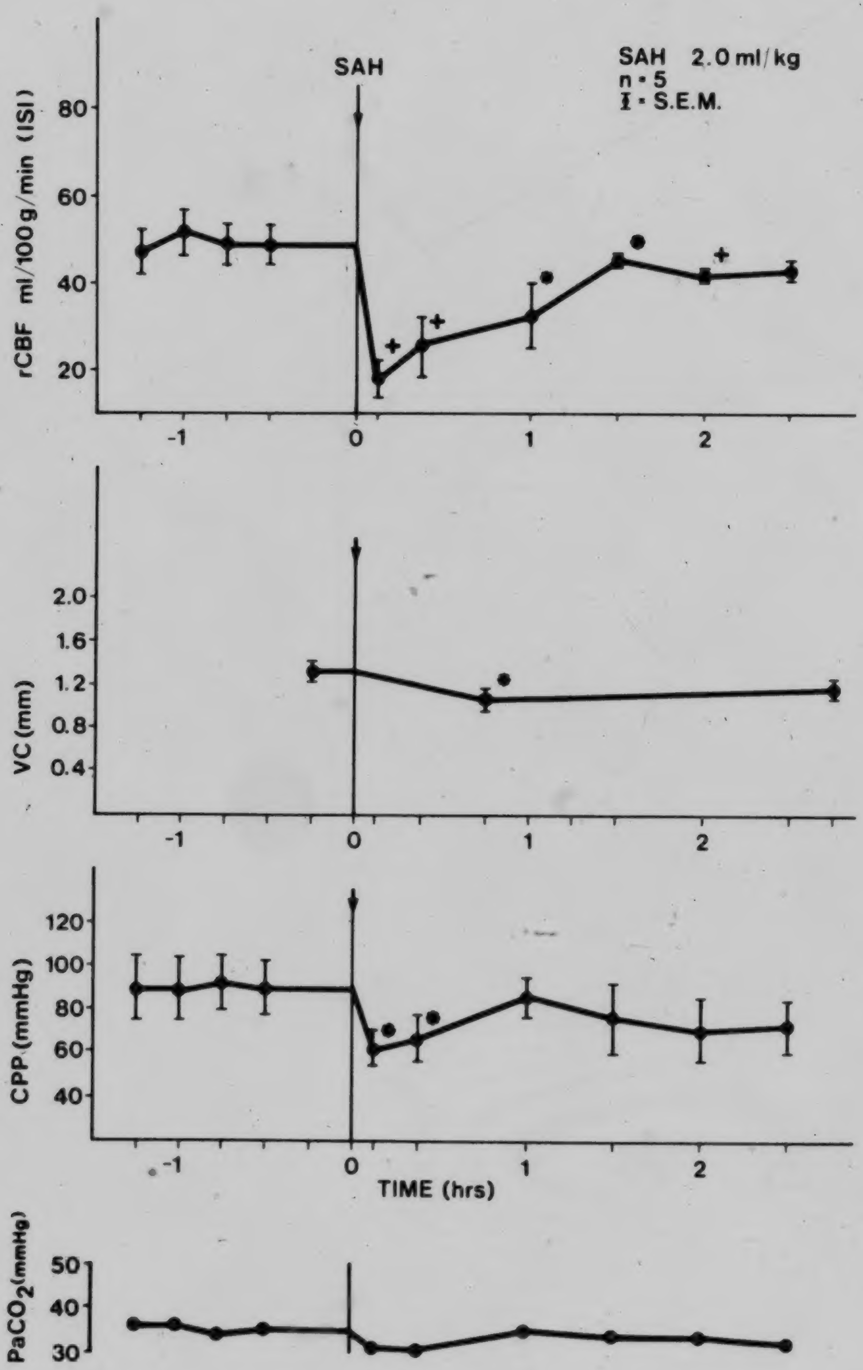


Figure 17: Pre and post-SAH rCBF, VC (vessel caliber), CPP and $PaCO_2$ for the 2.0 ml/kg SAH group.

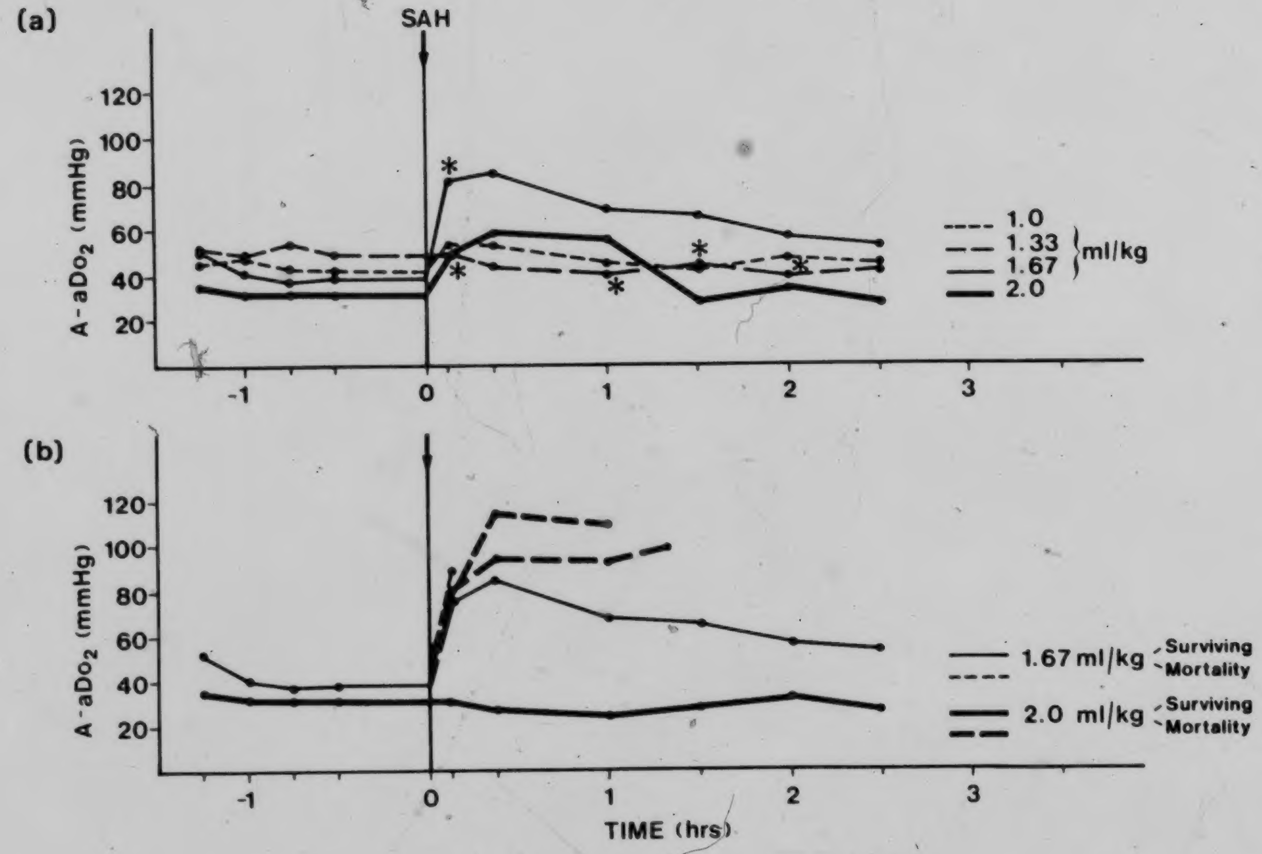


Figure 18: Pre and post-SAH A-aDO$_2$.

(a) for all animals in the 4 SAH volume groups.

(b) for those animals surviving the 5 hour observation period, and those dying within this time, in the 1.67 and 2.0 ml/kg SAH groups.

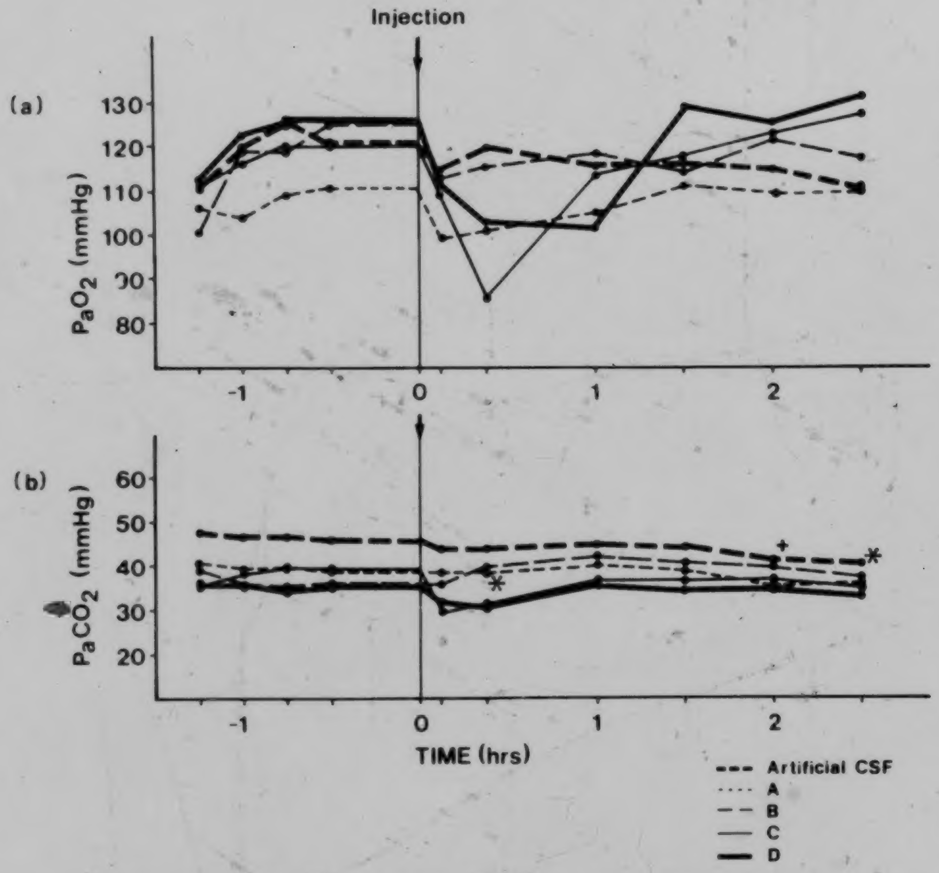


Figure 19: (a) Pre and post-insult PaO_2 for the 4 SAH volume groups and the artificial CSF group.

(b) Pre and post-insult $PaCO_2$ for the 4 SAH volume groups and the artificial CSF group.

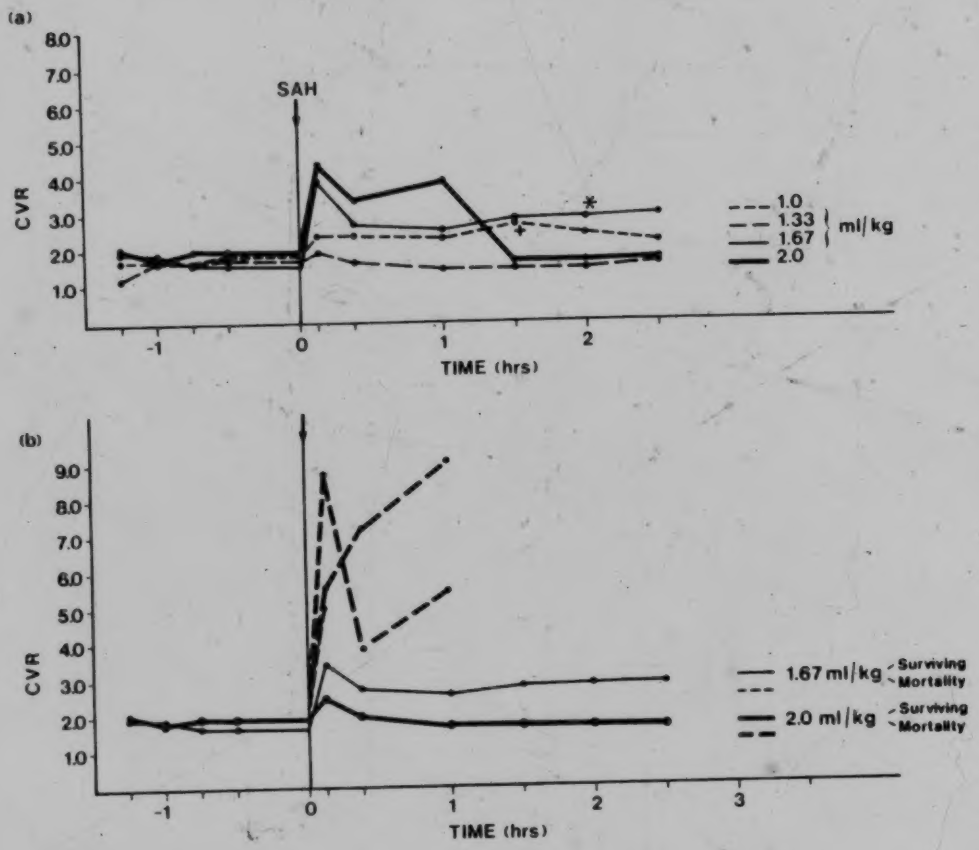


Figure 20: Pre and post-insult CVR.

(a) for all animals in the 4 SAH volume groups.

(b) for those animals surviving the 5 hour observation period, and those dying within this time, in the 1.67 and 2.0 ml/kg SAH groups.

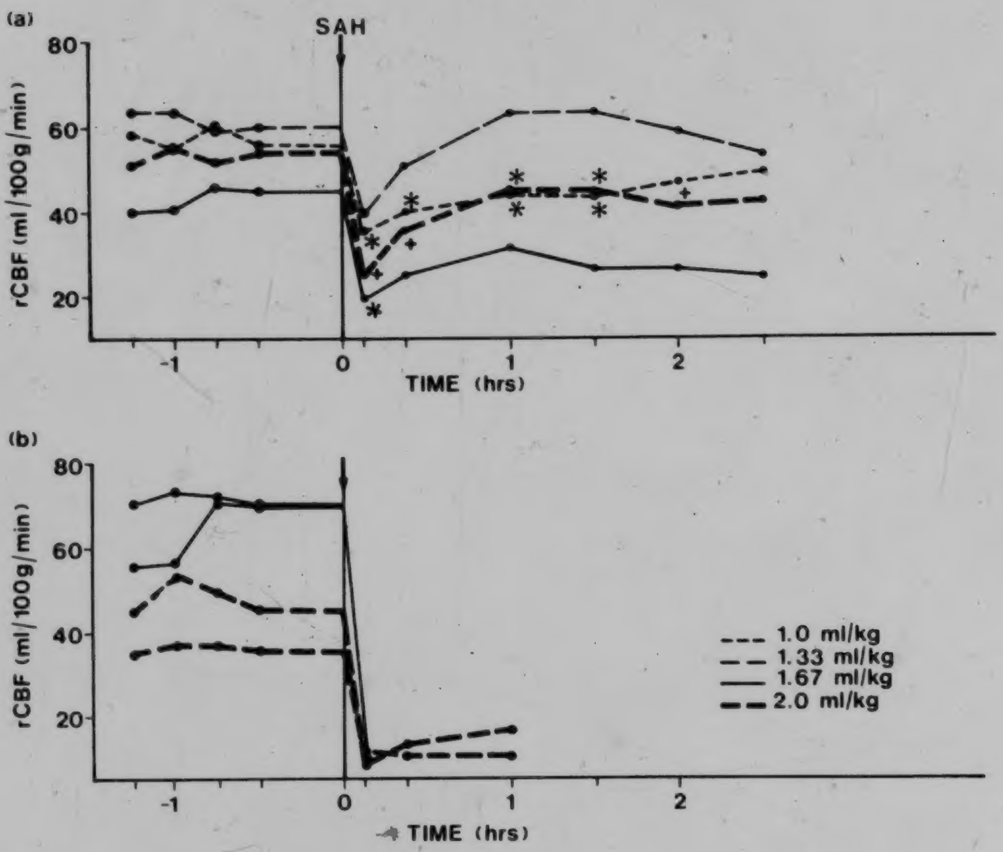


Figure 21: (a) Pre and post-SAH rCBF for those animals surviving the 5 hour observation period in the 4 SAH volume groups.

(b) Pre and post-SAH rCBF for those animals in the 1.67 and 2.0 ml/kg SAH groups dying before the 5 hour post-SAH limit.

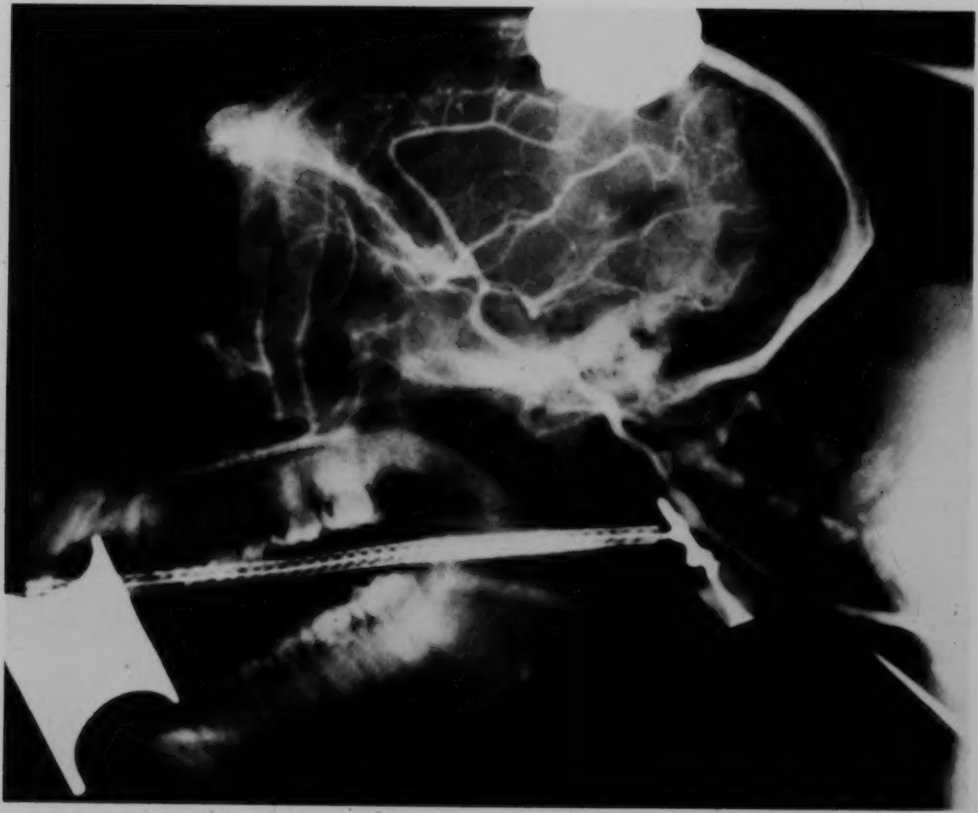


Figure 22: Lateral cerebral angiogram showing position of common carotid artery catheter, with its tip at the origin of the internal carotid artery; and the aneurysm clip occlusion of the external carotid artery at its origin.

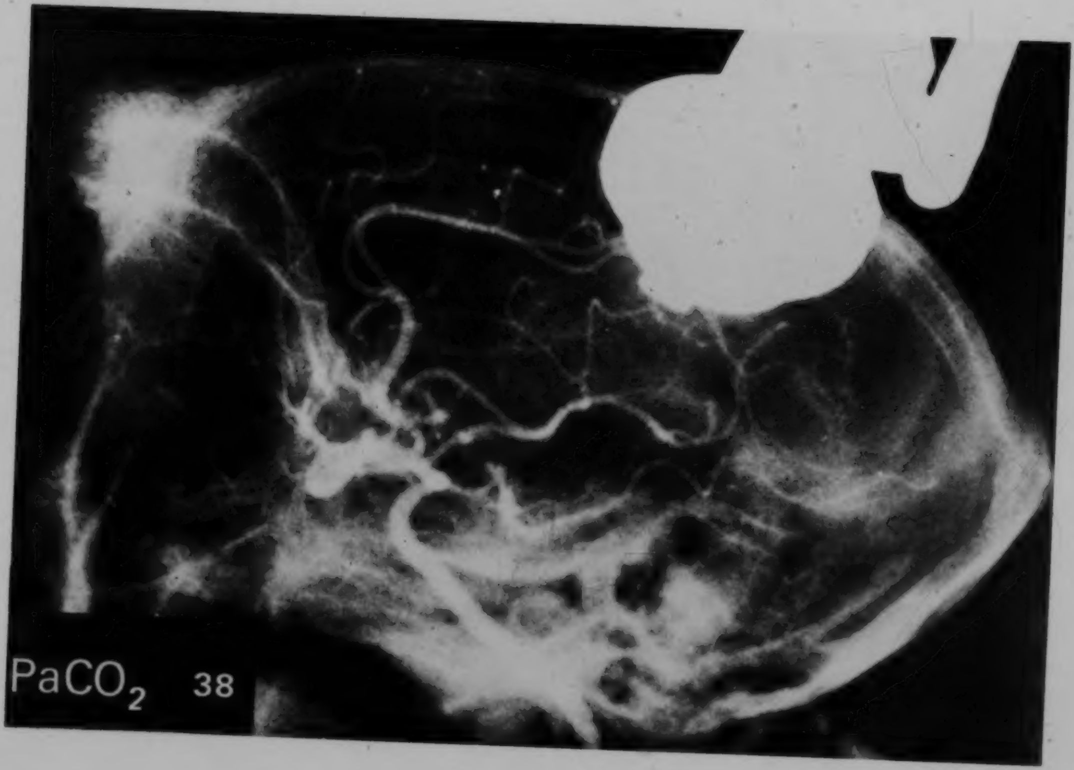


Figure 23 (a): Pre-SAH lateral cerebral angiogram for the 1.0 ml/kg SAH group.

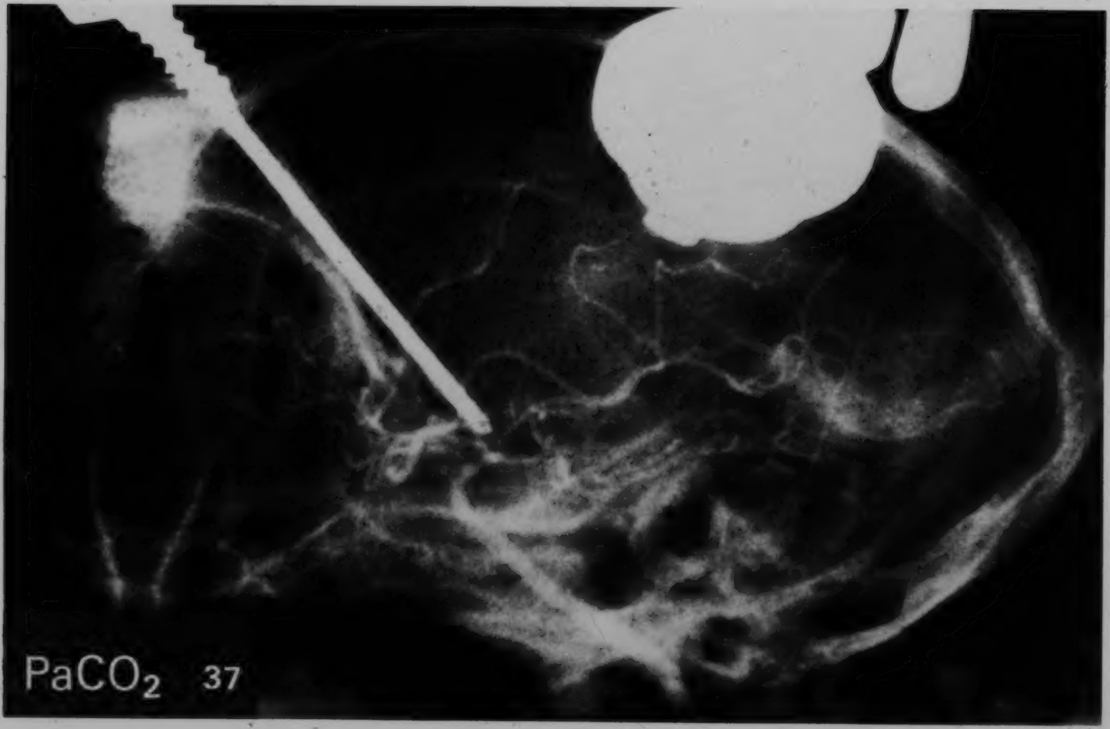


Figure 23 (b): Post-SAH (43 minutes) lateral cerebral angiogram for the 1.0 ml.kg SAH group.

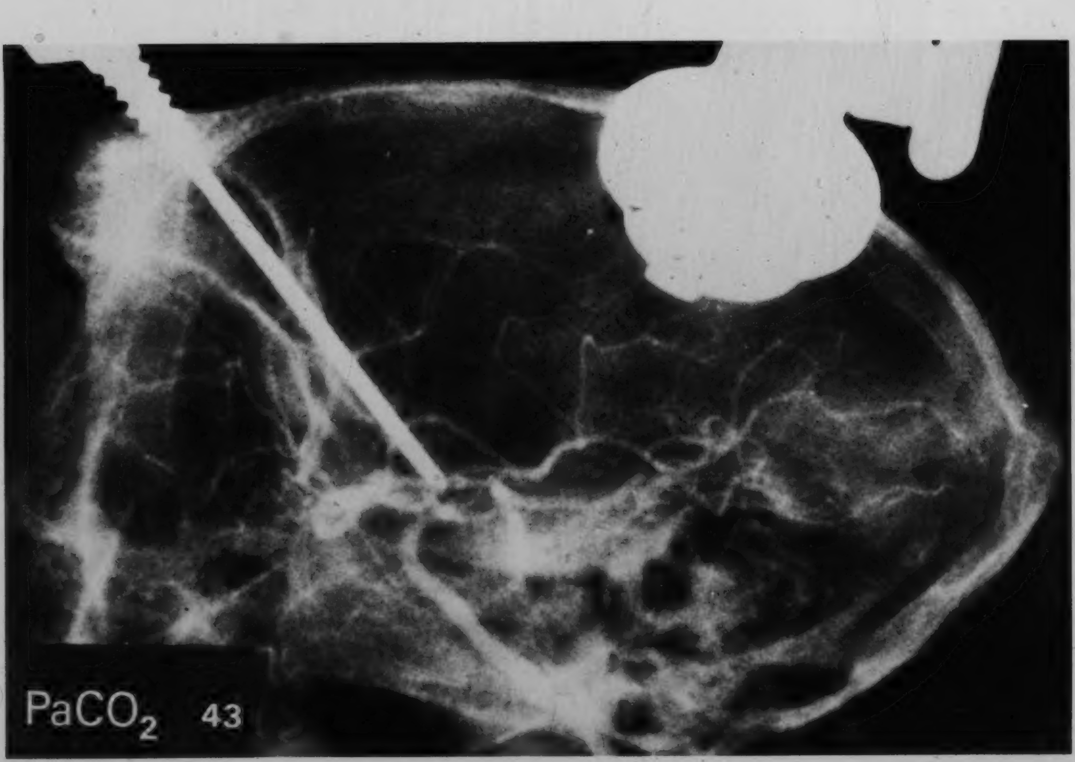


Figure 23 (c): Post-SAH (175 minutes) lateral cerebral angiogram for the 1.0 ml/kg SAH group.

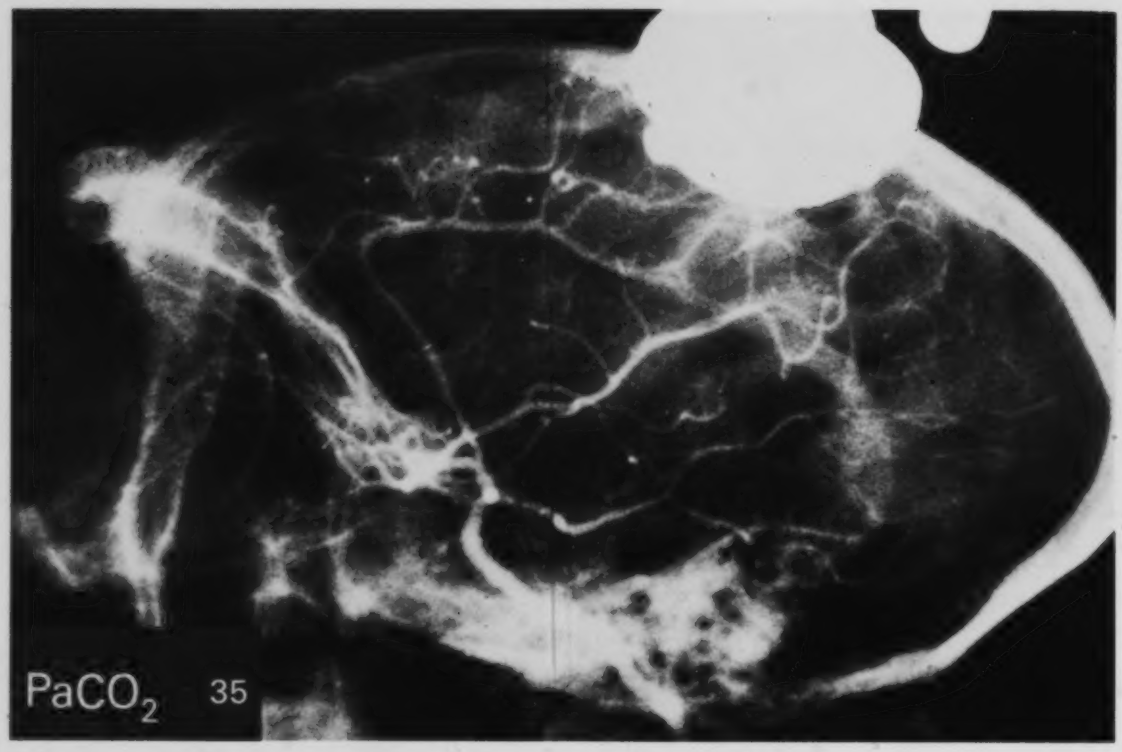


Figure 24 (a): Pre-SAH lateral cerebral angiogram for the 1.33 ml/kg SAH group.

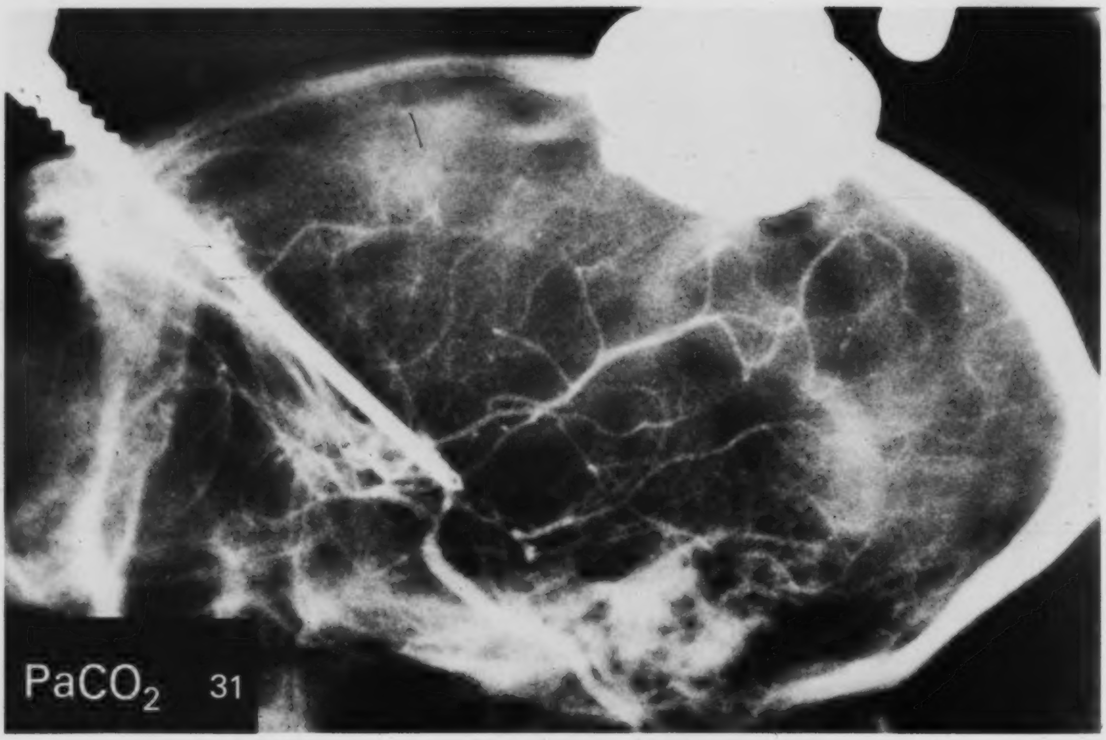


Figure 24 (b): Post-SAH (42 minutes) lateral cerebral angiogram for the 1.33 ml/kg SAH group.

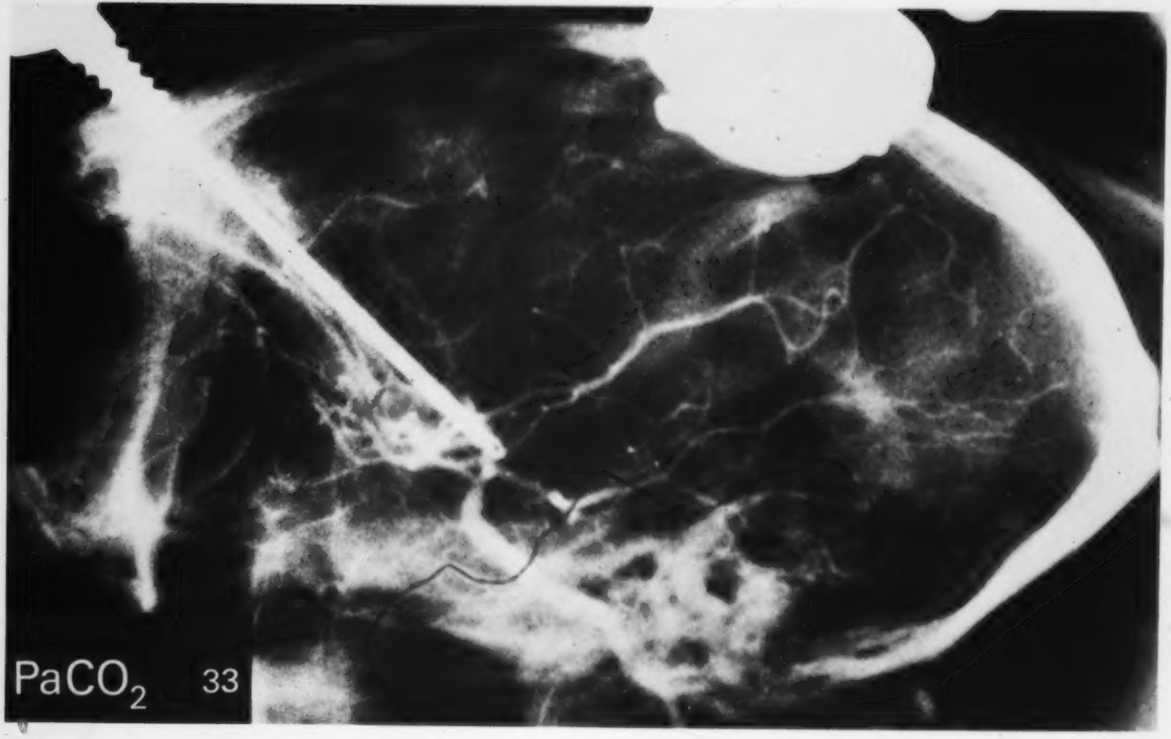


Figure 24 (c): Post-SAH (164 minutes) lateral cerebral angiogram for the 1.33 ml/kg SAH group.

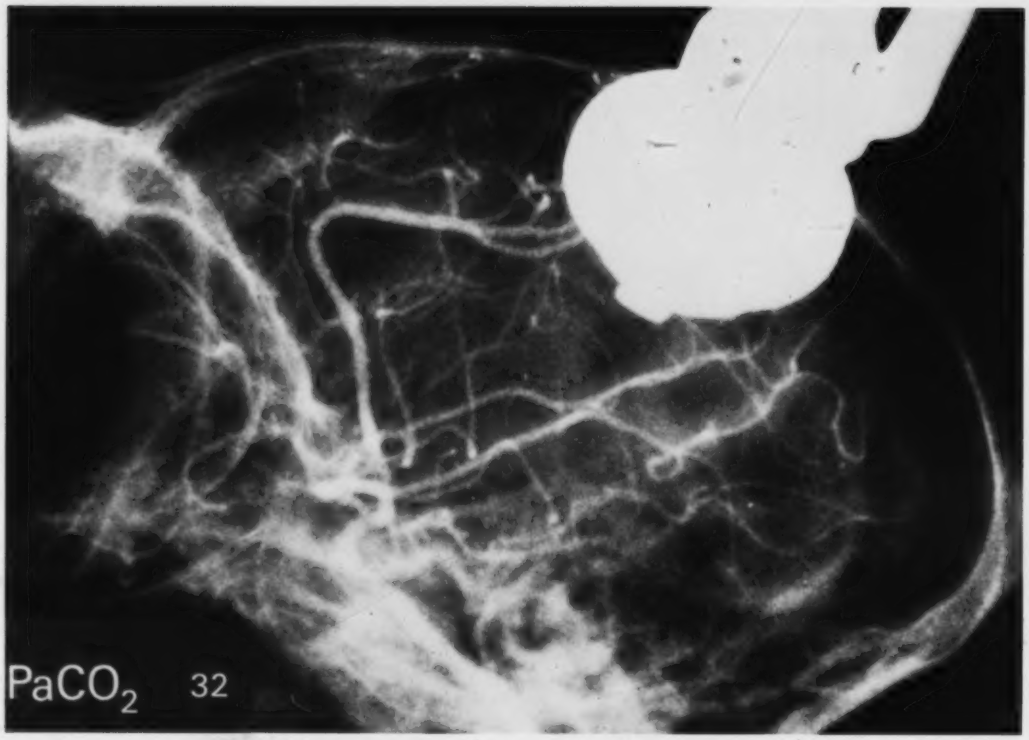


Figure 25 (a): Pre-SAH lateral cerebral angiogram for the 1.67 ml/kg SAH group.

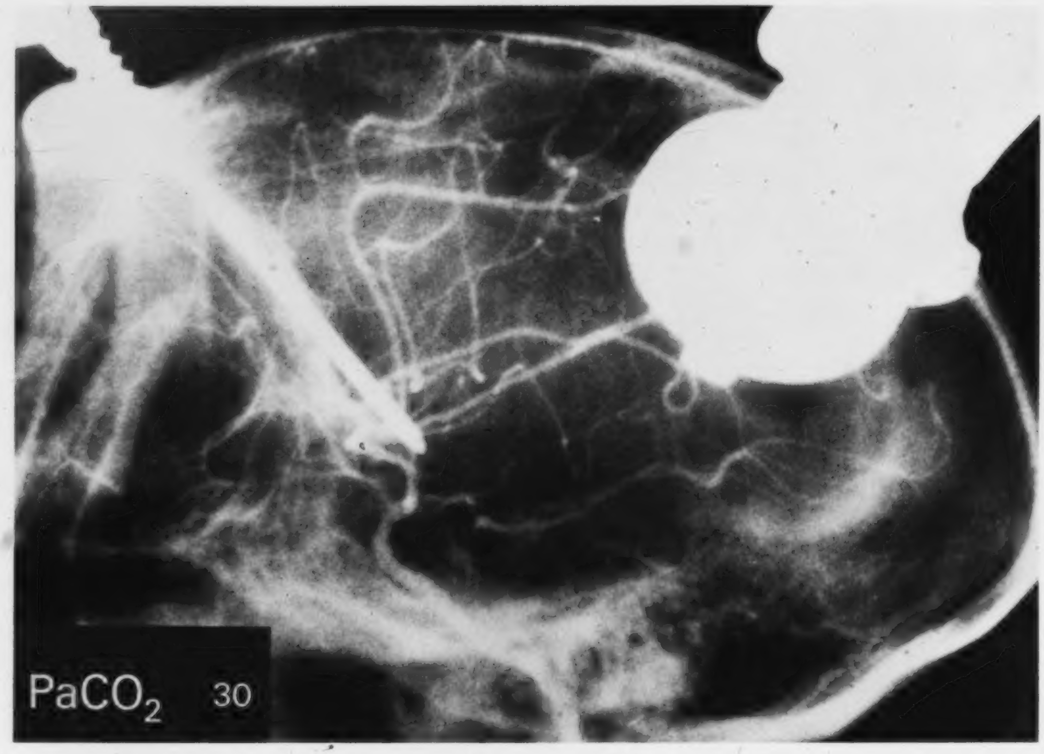


Figure 25 (b): Post-SAH (43 minutes) lateral cerebral angiogram for the 1.67 ml/kg SAH group.

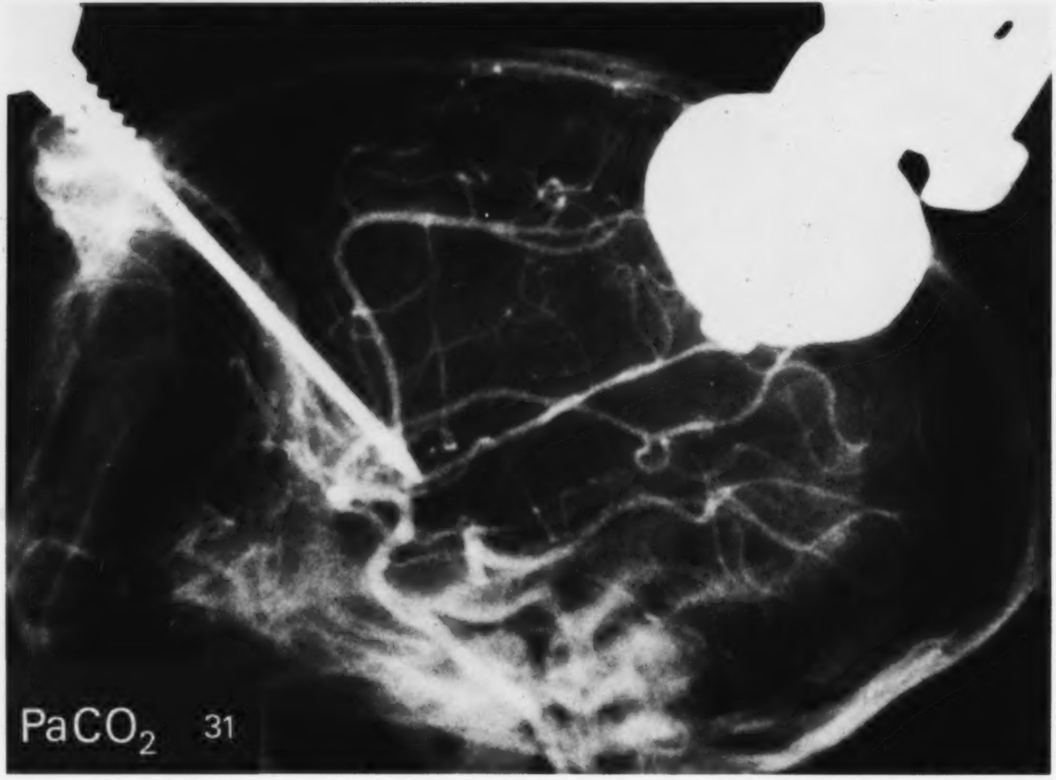


Figure 25 (c): Post-SAH (173 minutes) lateral cerebral angiogram for the 1.67 ml/kg SAH group.

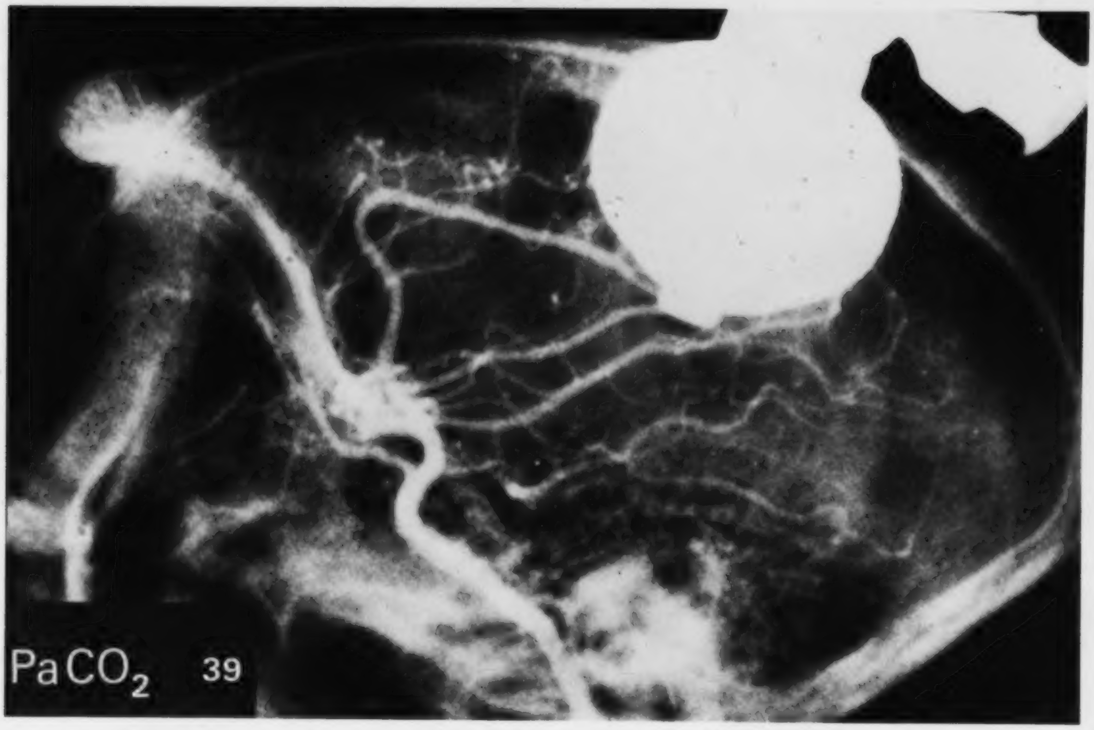


Figure 26 (a): Pre-SAH lateral cerebral angiogram for the 2.0 ml/kg SAH group.

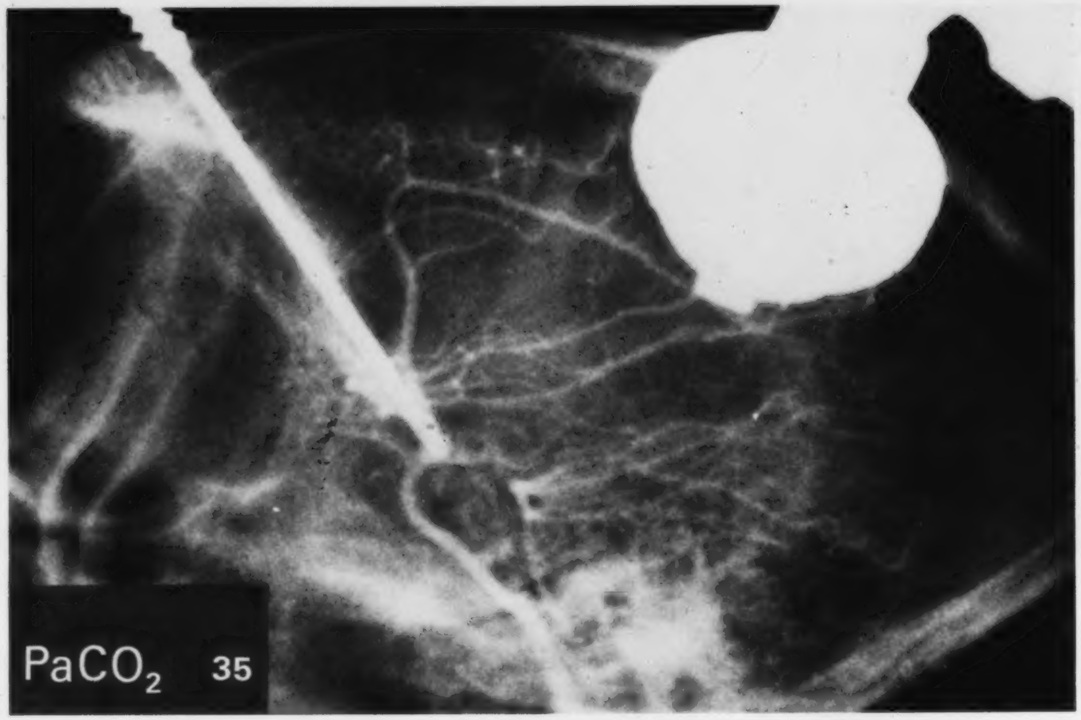


Figure 26 (b): Post-SAH (42 minutes) lateral cerebral angiogram for the 2.0 ml/kg SAH group.

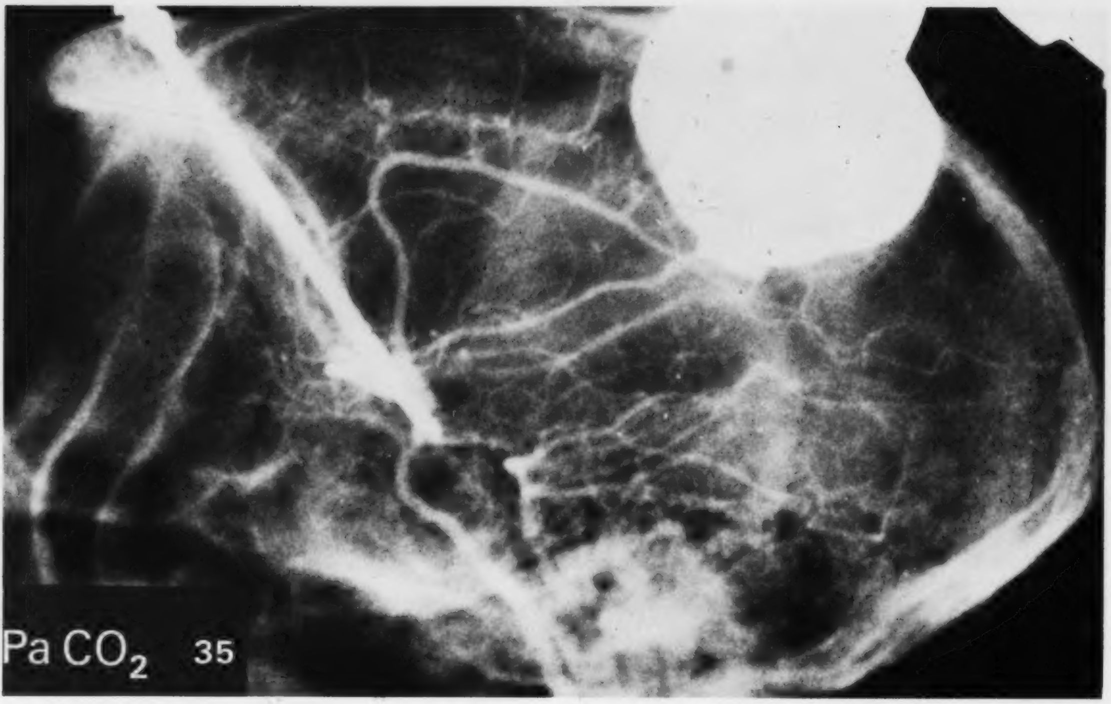


Figure 26 (c): Post-SAH (169 minutes) lateral cerebral angiogram for the 2.0 ml/kg SAH group.

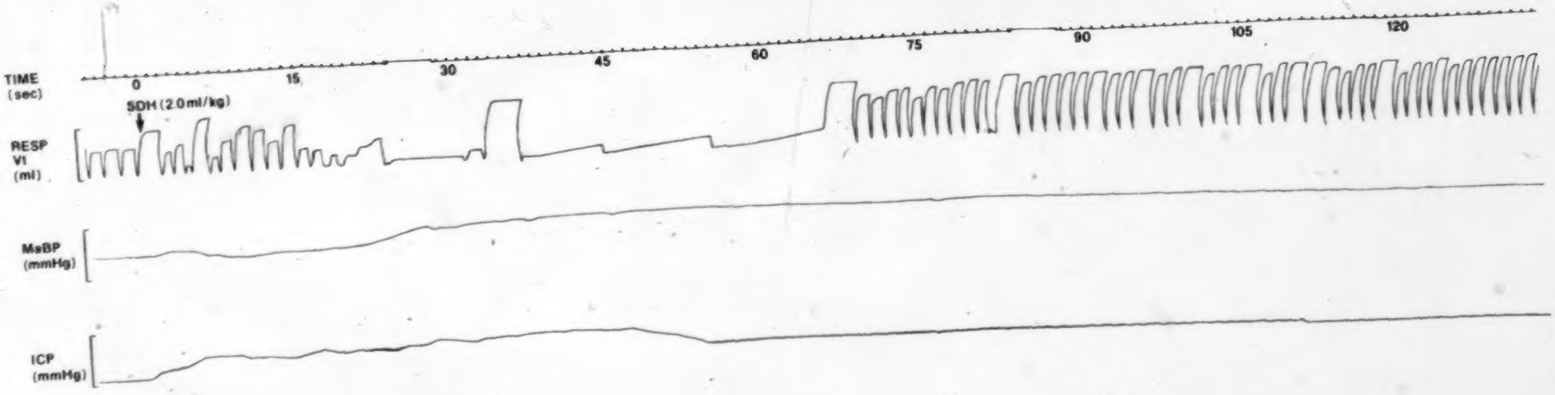


Figure 27: ICP, MaBP and respiratory responses to an induced SDH.

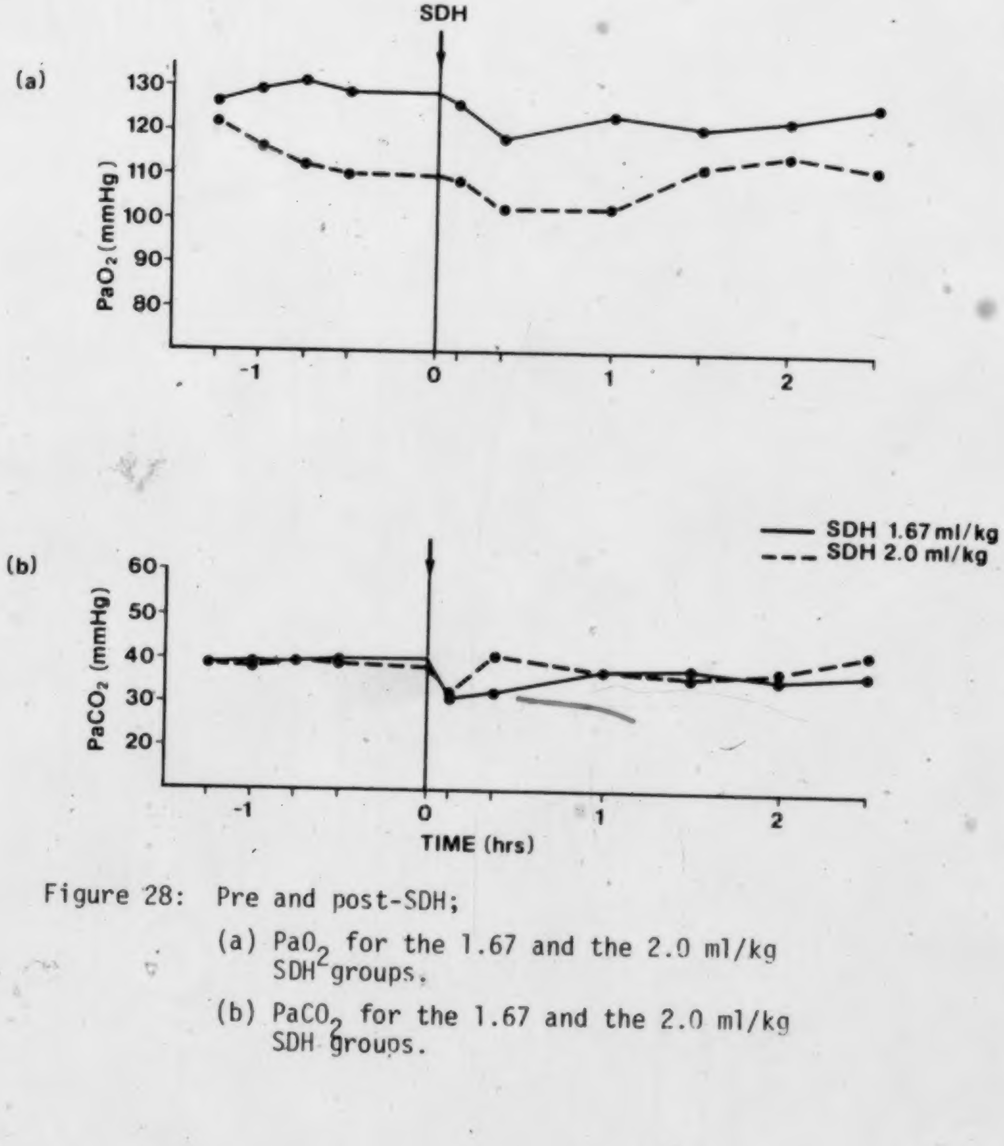


Figure 28: Pre and post-SDH;

(a) PaO_2 for the 1.67 and the 2.0 ml/kg SDH groups.

(b) $PaCO_2$ for the 1.67 and the 2.0 ml/kg SDH groups.

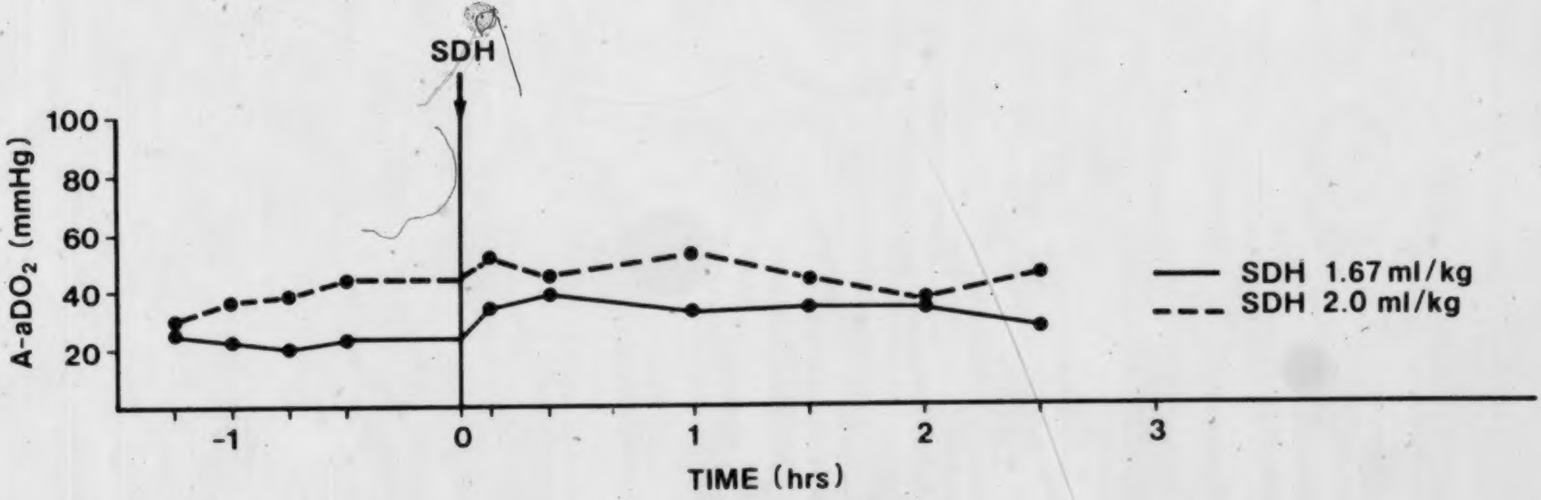


Figure 29: Pre and post-SDH A-aDO$_2$ for the 1.67 and the 2.0 ml/kg groups.

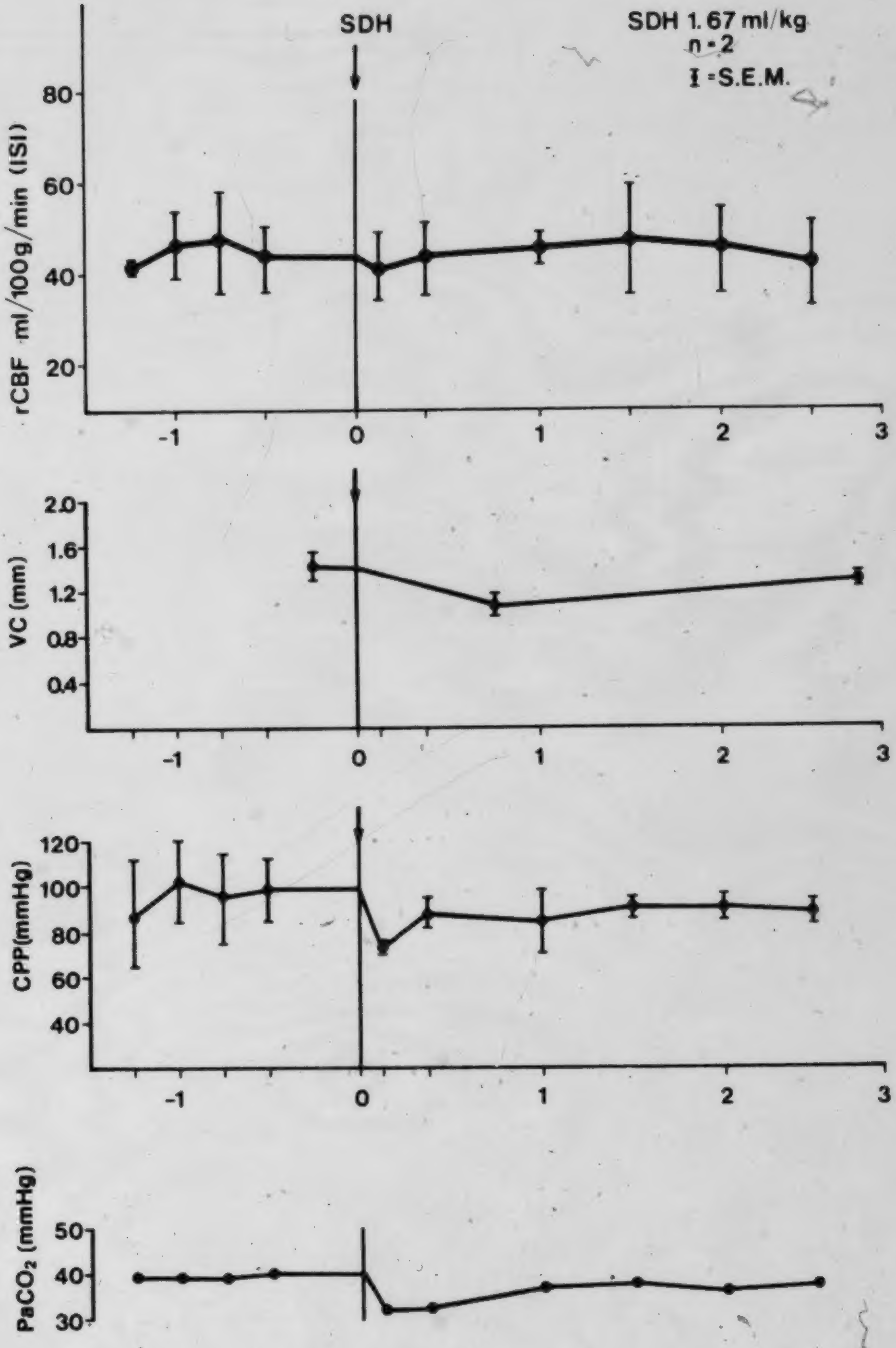


Figure 30: Pre and post-SDH rCBF, VC (vessel caliber), CPP and $PaCO_2$ for the 1.67 ml/kg SDH group.

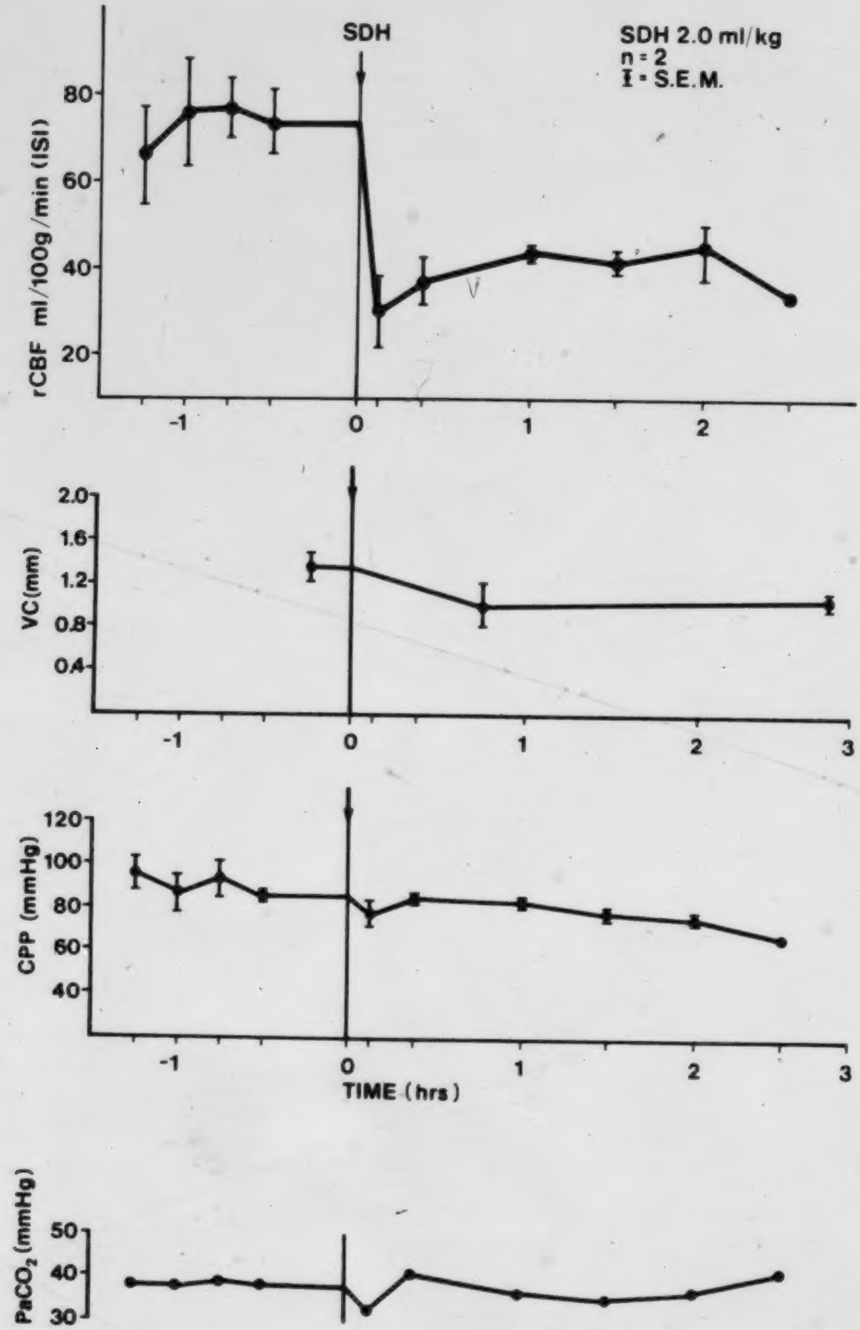


Figure 31: Pre and post-SDH rCBF, VC (vessel caliber), CPP and $PaCO_2$ for the 2.0 ml/kg SDH group.

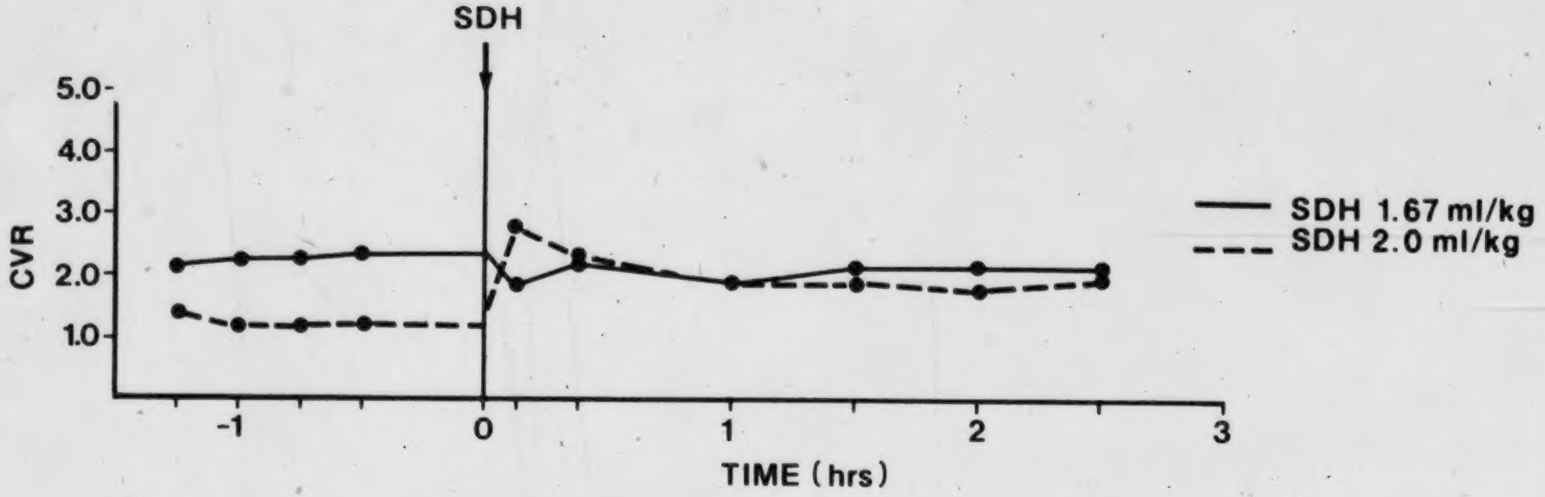


Figure 32: Pre and post-SDH CVR for the 1.67 and the 2.0 ml/kg SDH groups.

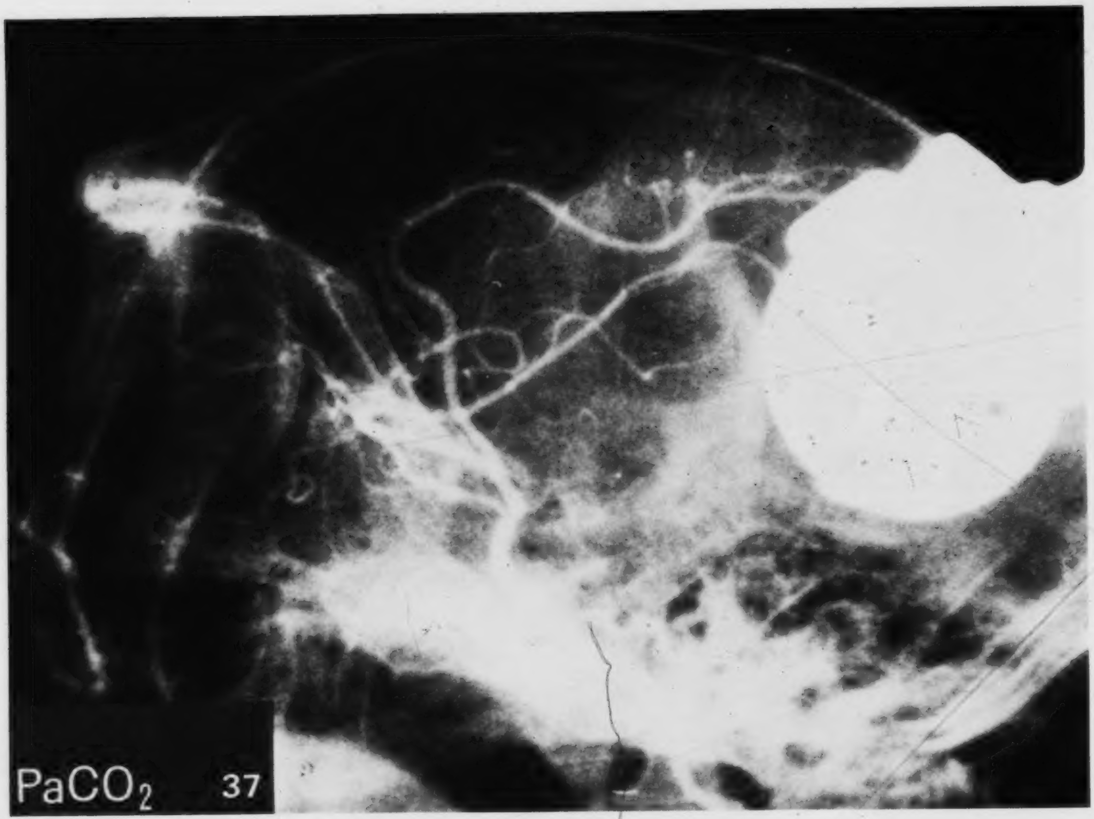


Figure 33 (a): Pre-SDH lateral cerebral angiogram for the 1.67 ml/kg SDH group.

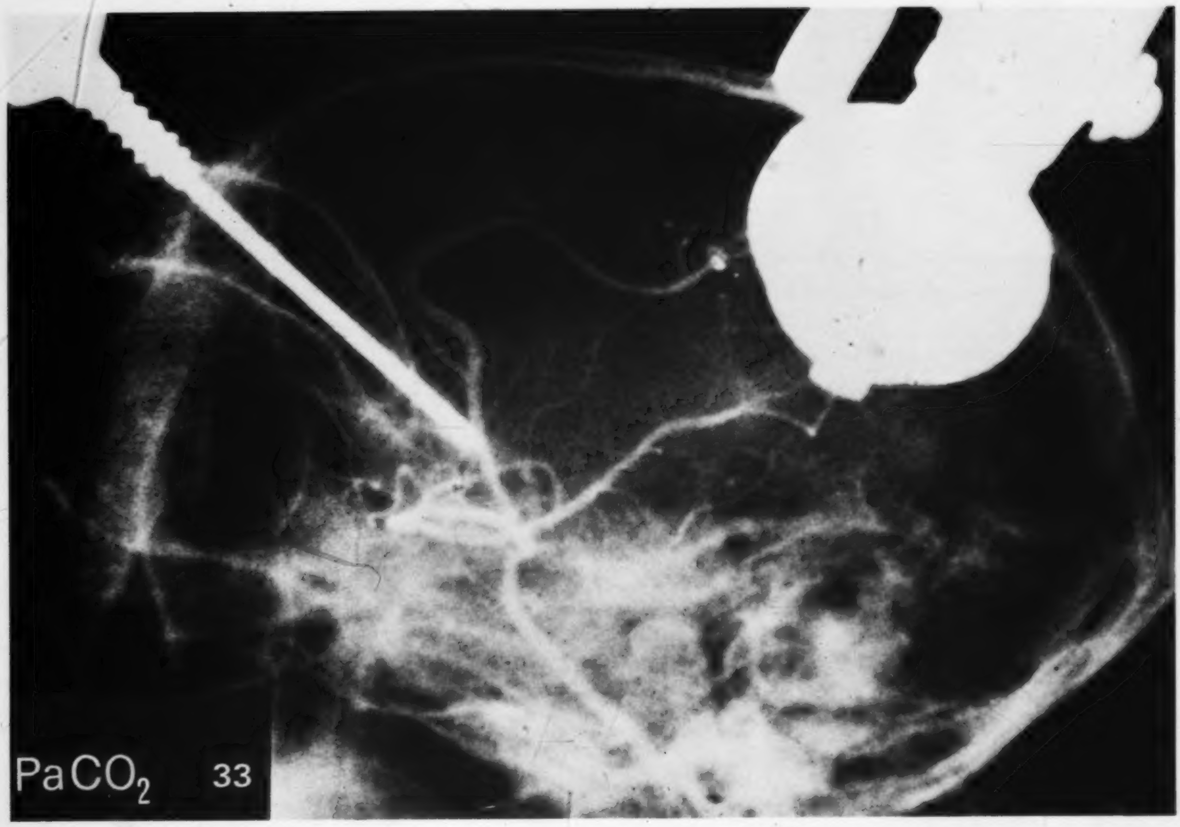


Figure 33 (b): Post-SDH (42 minutes) lateral cerebral angiogram for the 1.67 ml/kg SDH group.

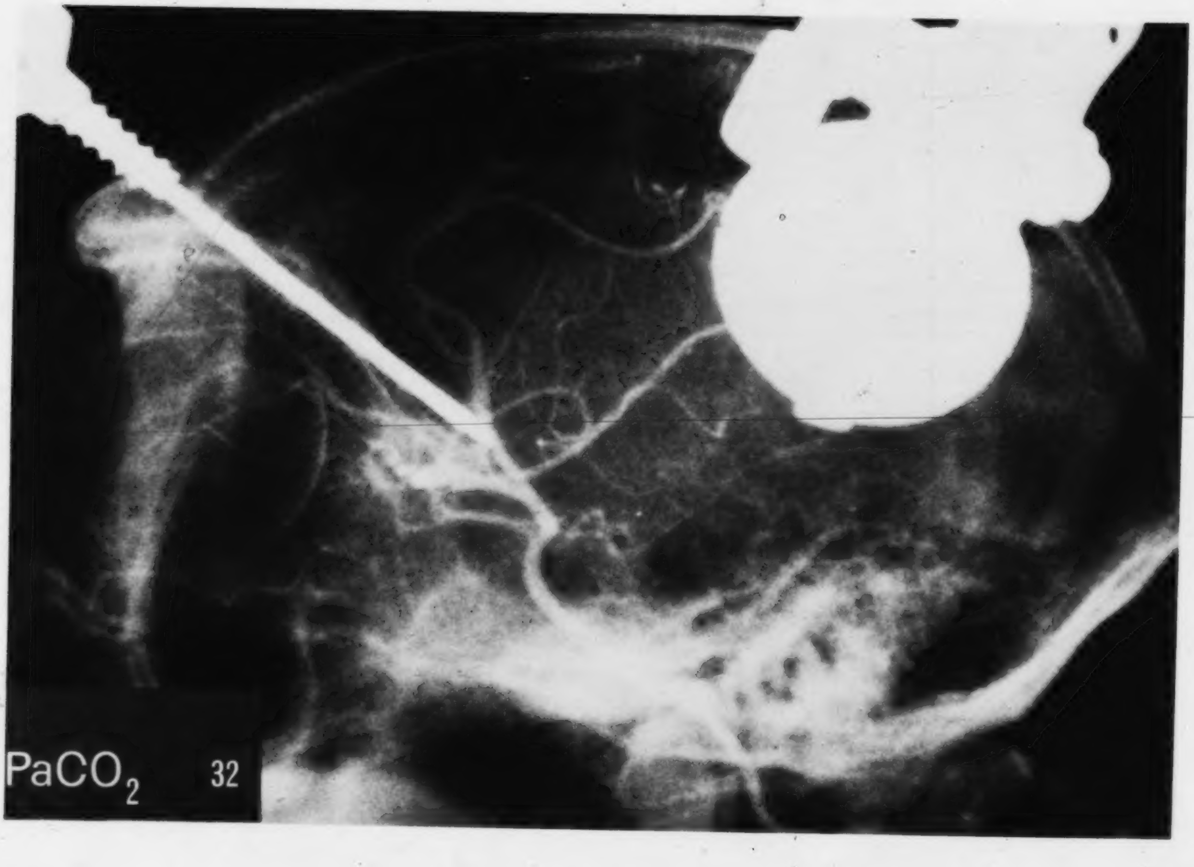


Figure 33 (c): Post-SDH (163 minutes) lateral cerebral angiogram for the 1.67 ml/kg SDH group.

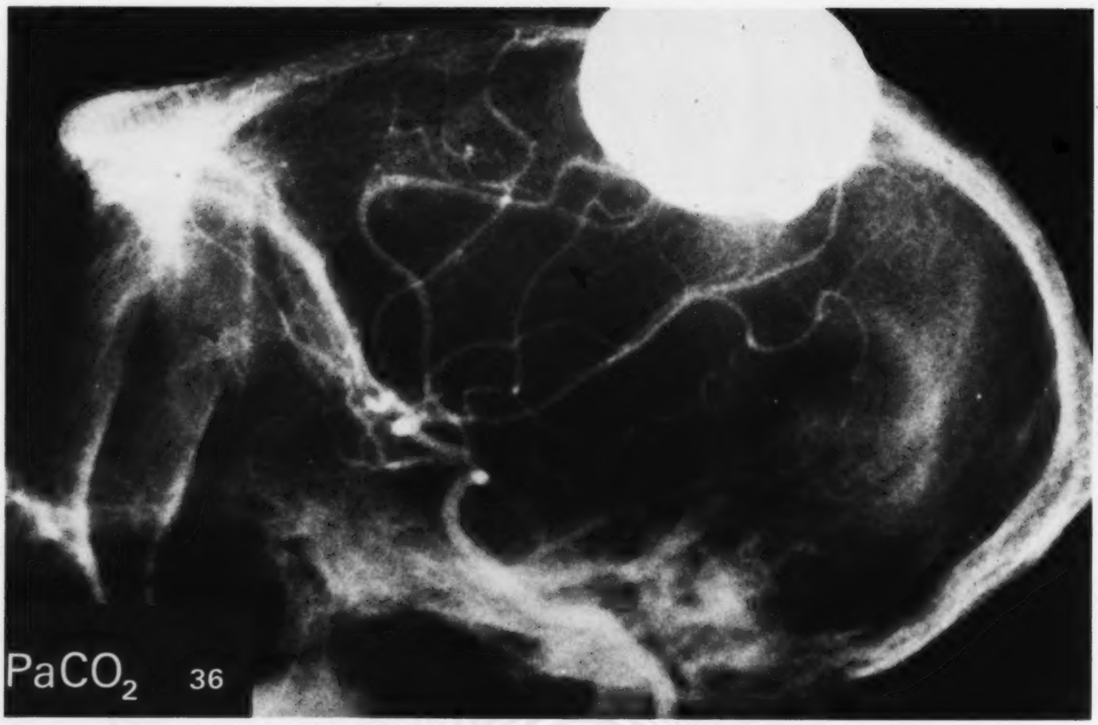


Figure 34 (a): Pre-SDH lateral cerebral angiogram for the 2.0 ml/kg SDH group.

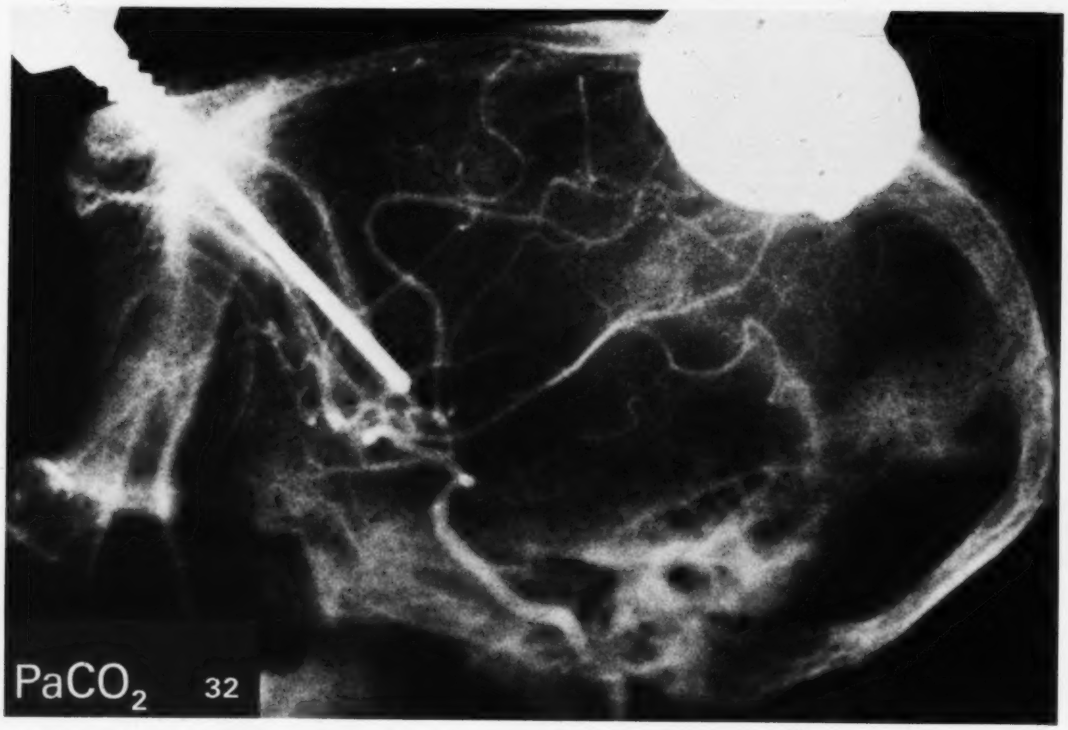


Figure 34 (b): Post-SDH (52 minutes) lateral cerebral angiogram for the 2.0 ml/kg SDH group.

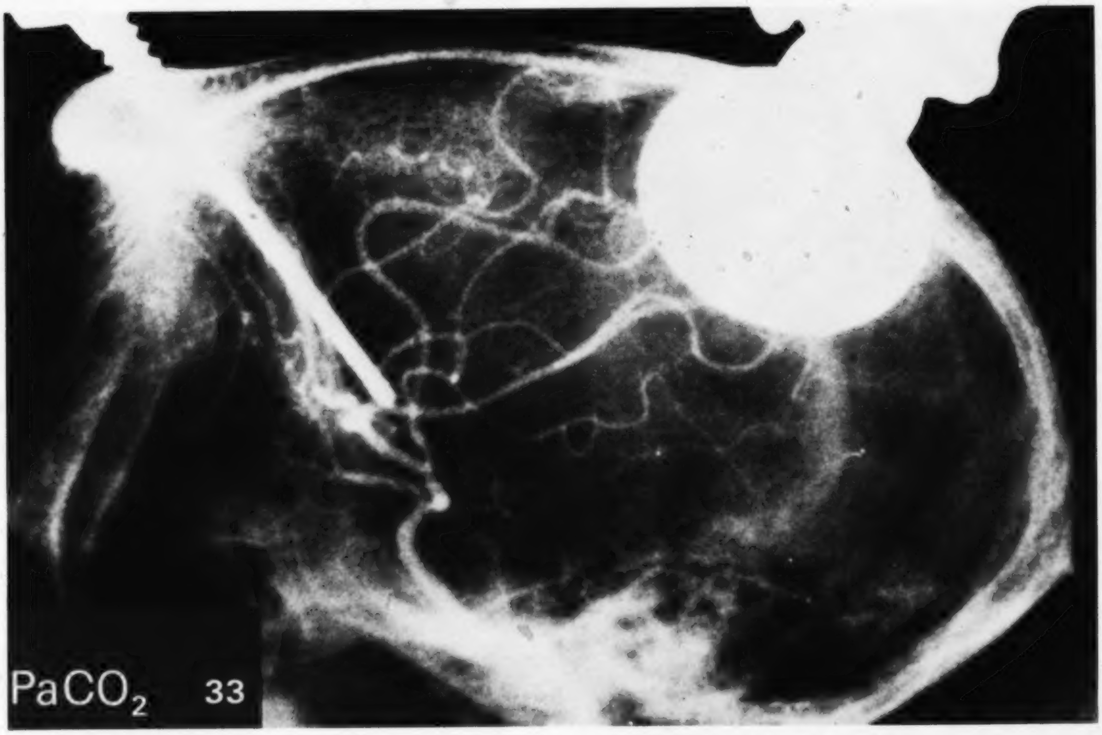


Figure 34 (c): Post-SDH (177 minutes) lateral cerebral angiogram for the 2.0 ml/kg SDH group.

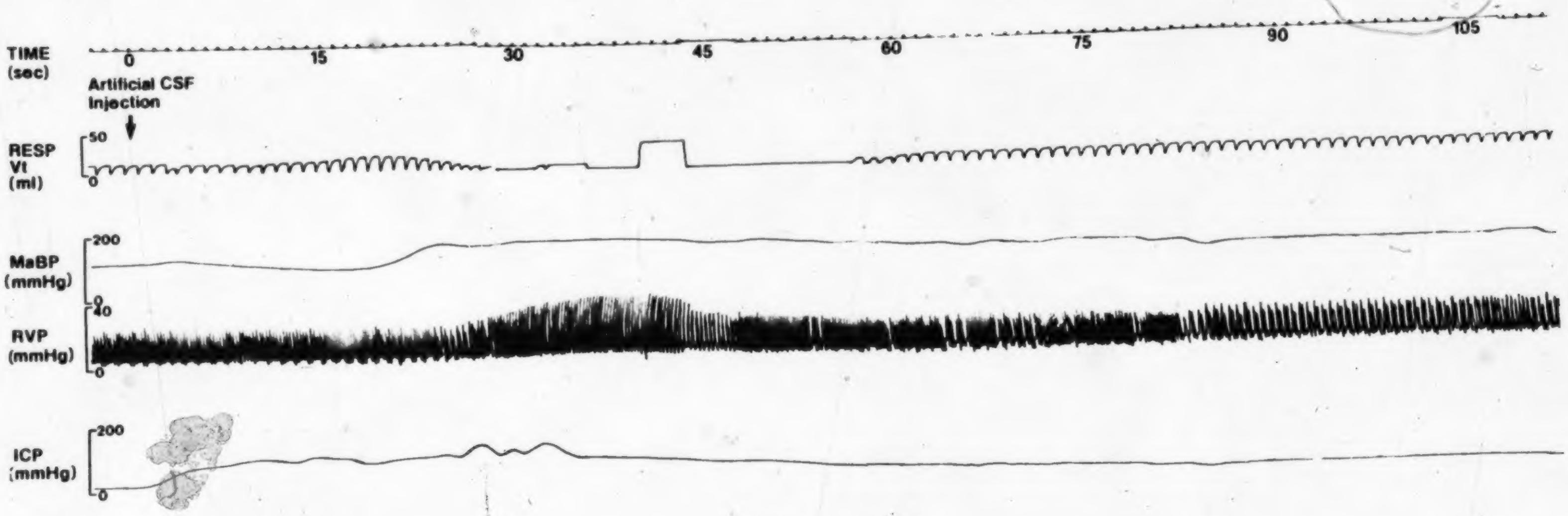


Figure 35: ICP, MaBP, respiratory pattern and RVP responses to a subarachnoid injection of artificial CSF.

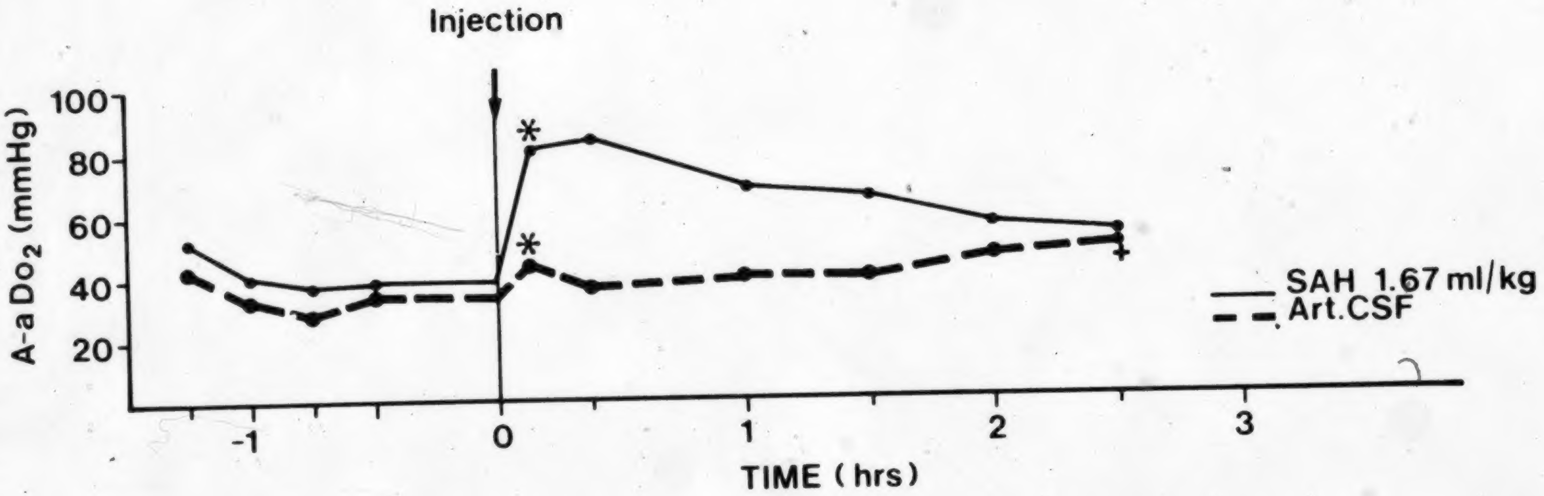


Figure 36: Pre and post-insult A-aDO$_2$ for the 1.67 ml/kg SAH group and the artificial CSF group.

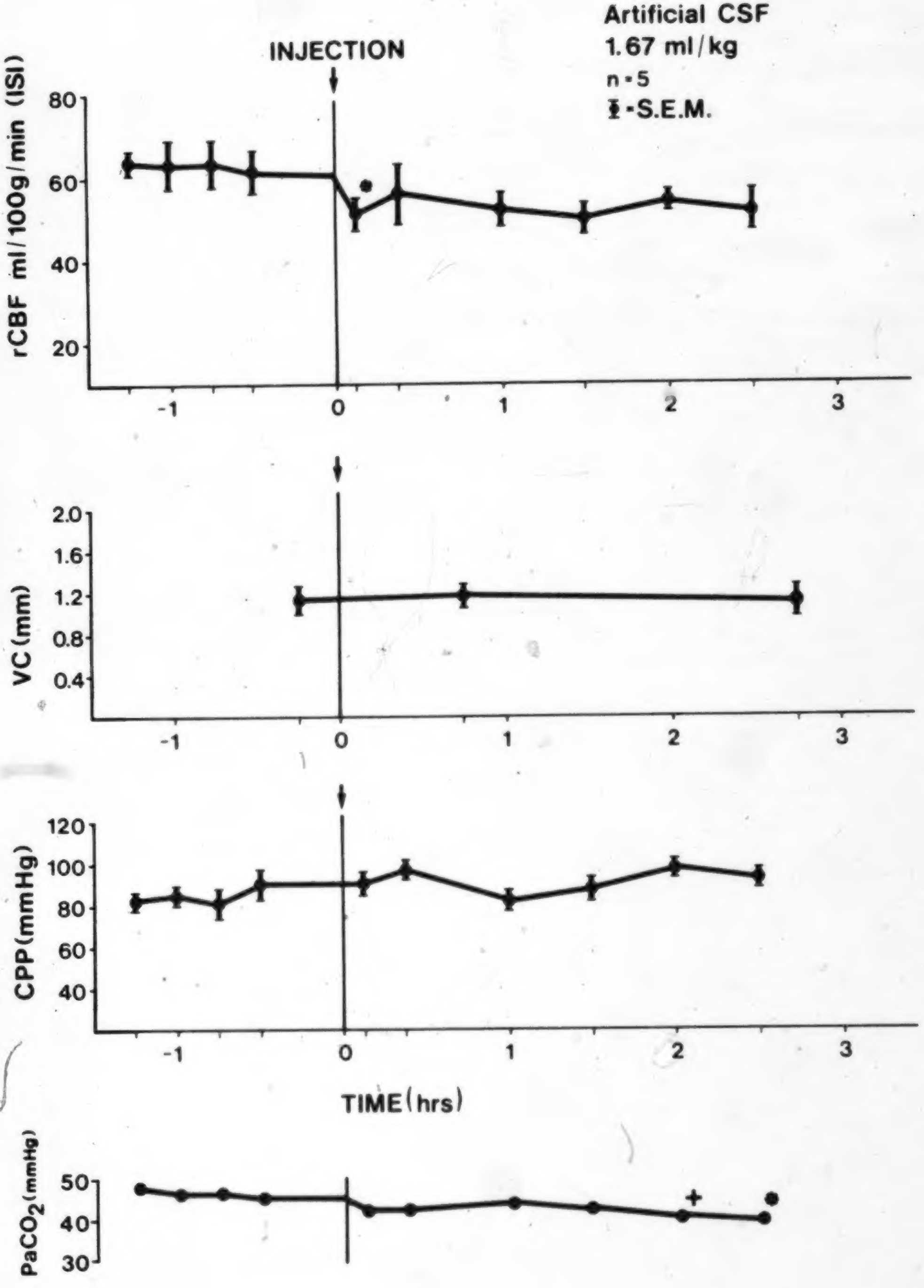


Figure 37: Pre and post-insult rCBF, VC (vessel caliber), CPP and $PaCO_2$ for the artificial CSF group.

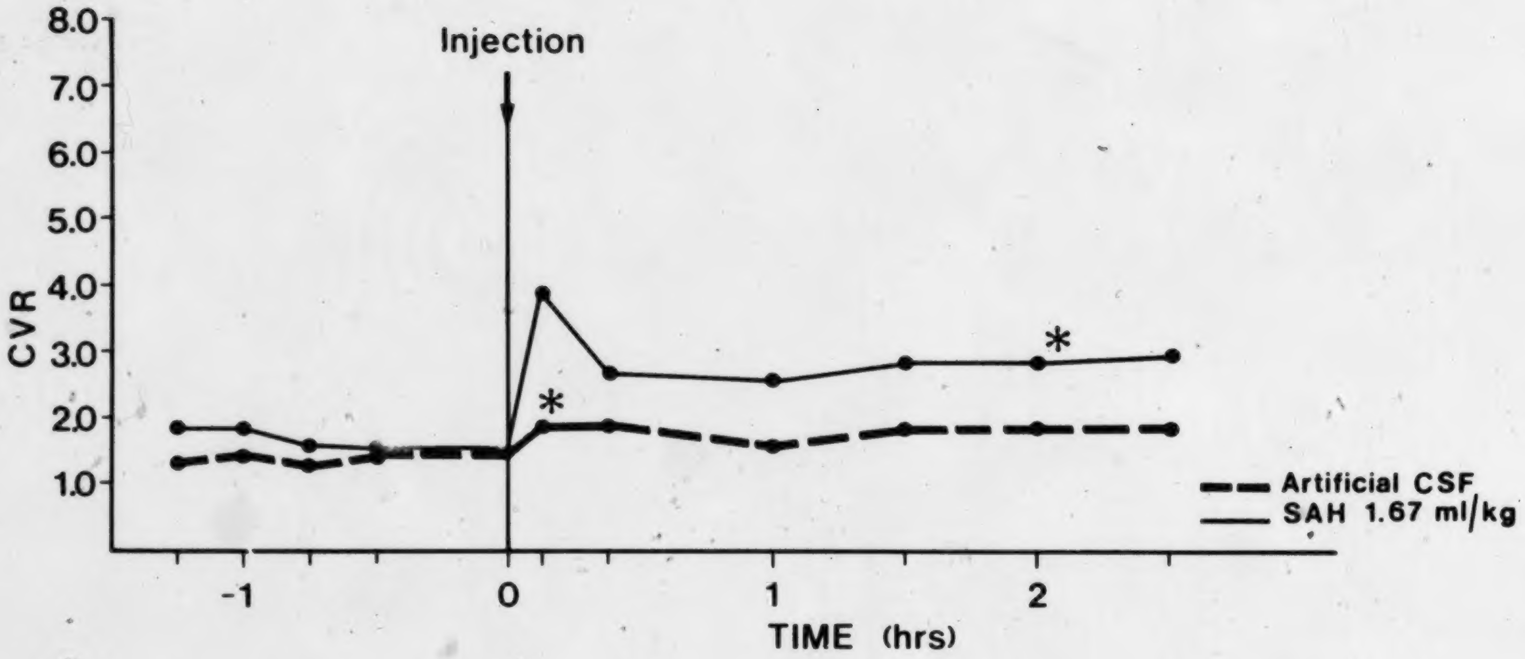


Figure 38: Pre and post-insult CVR for the 1.67 ml/kg SAH group and the artificial CSF group.

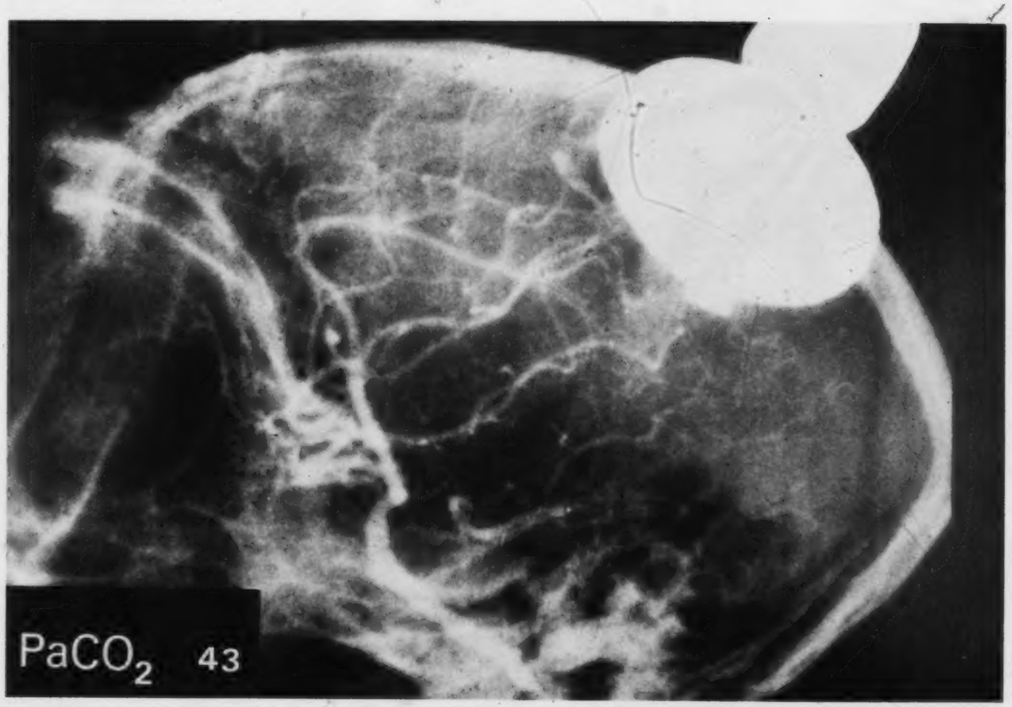


Figure 39 (a): Pre-insult lateral cerebral angiogram for the artificial CSF group.

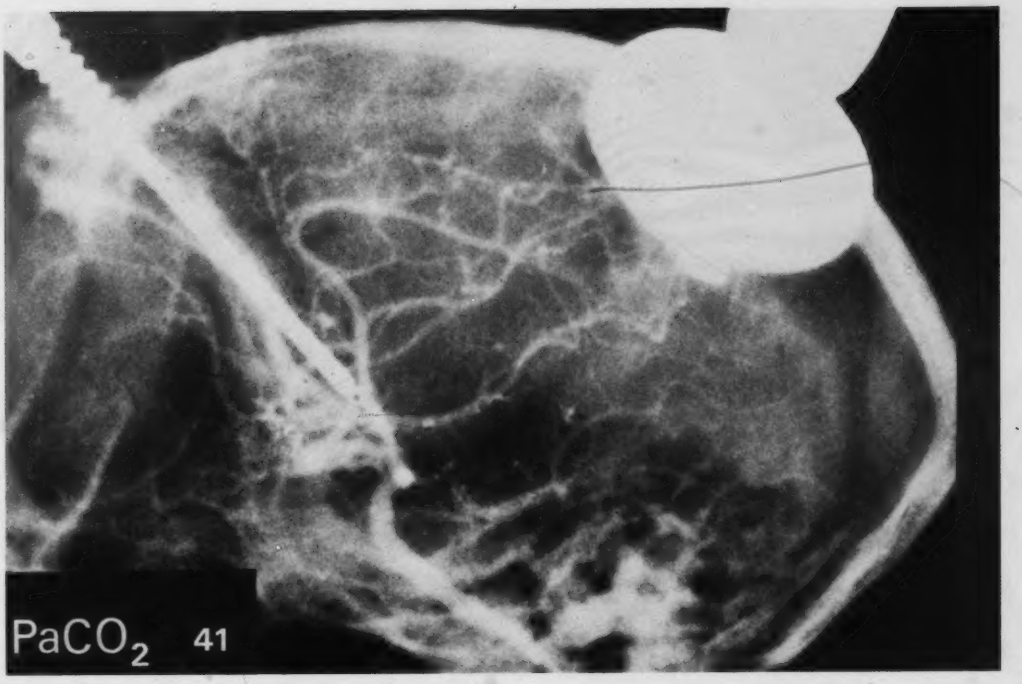


Figure 39 (b): Post-insult (41 minutes) lateral cerebral angiogram for the artificial CSF group.

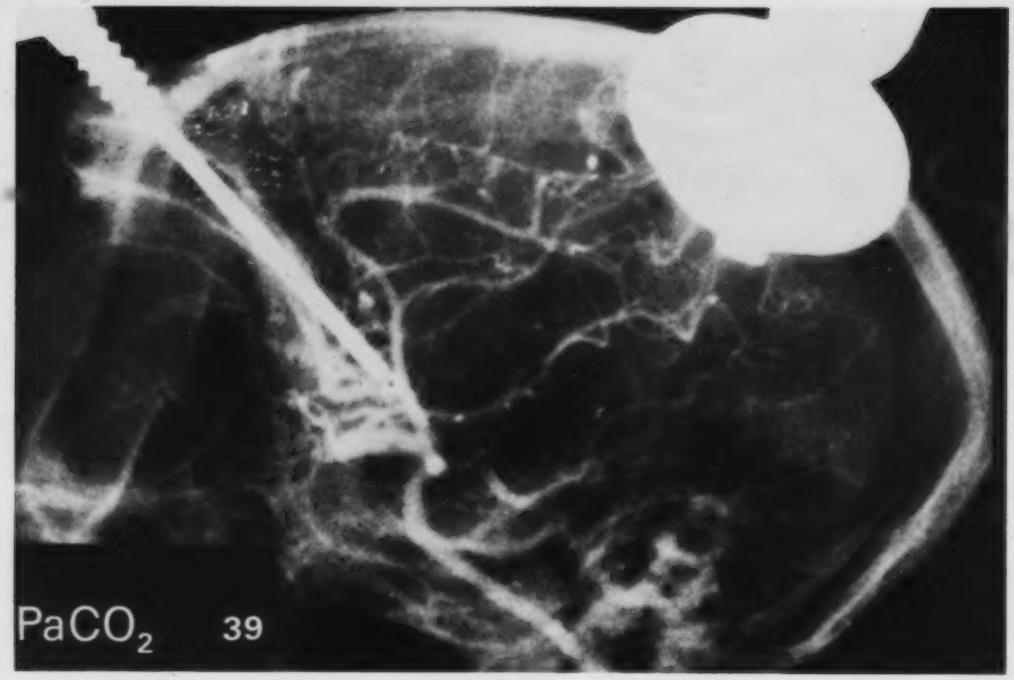


Figure 39 (c): Post-insult (166 minutes) lateral angiogram for the artificial CSF group.

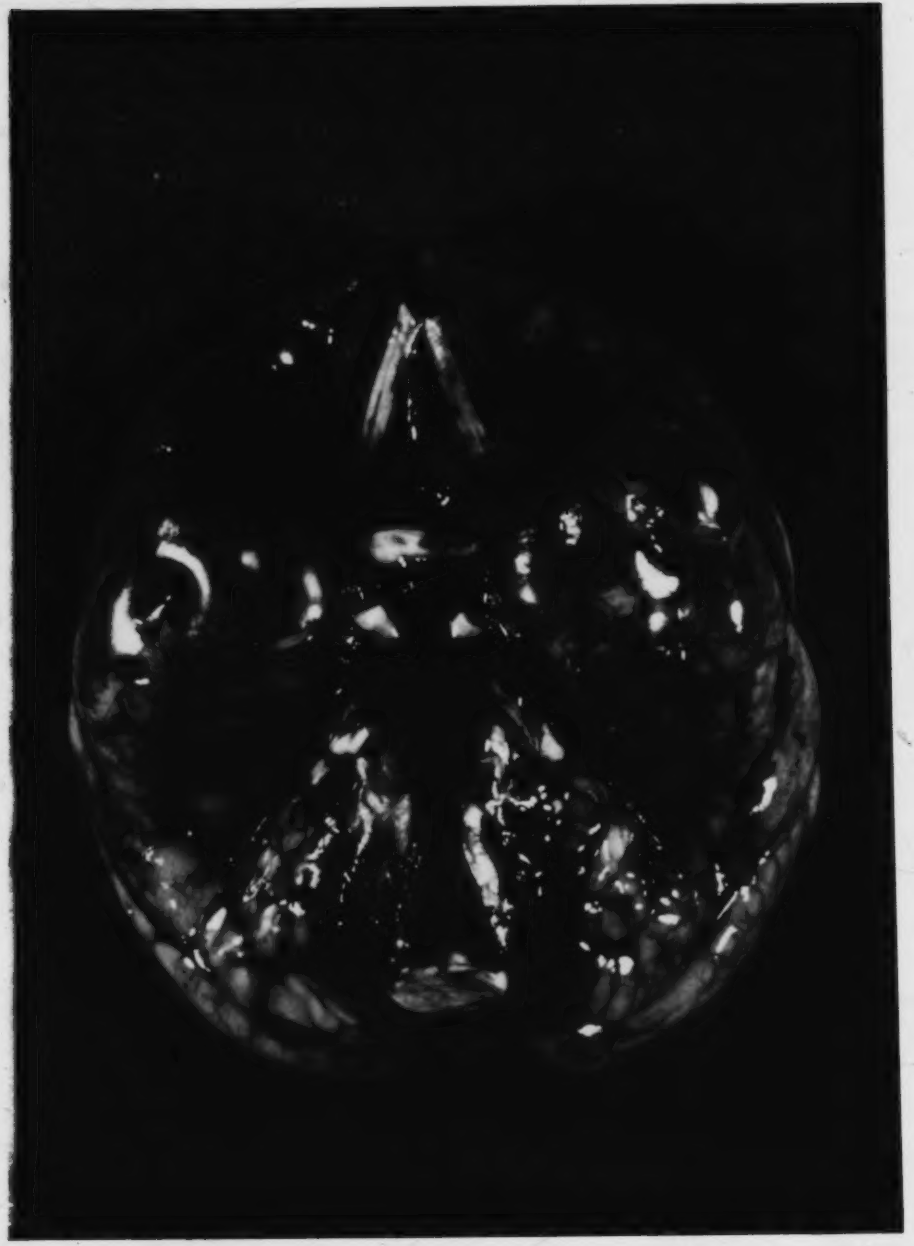


Figure 40: Subarachnoid hemorrhage - basal view.

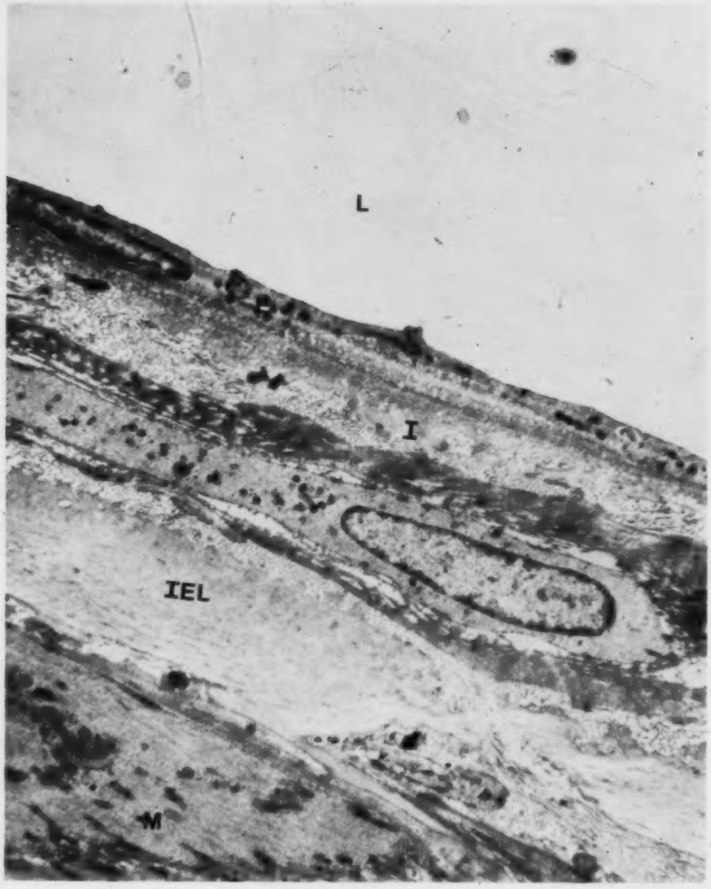
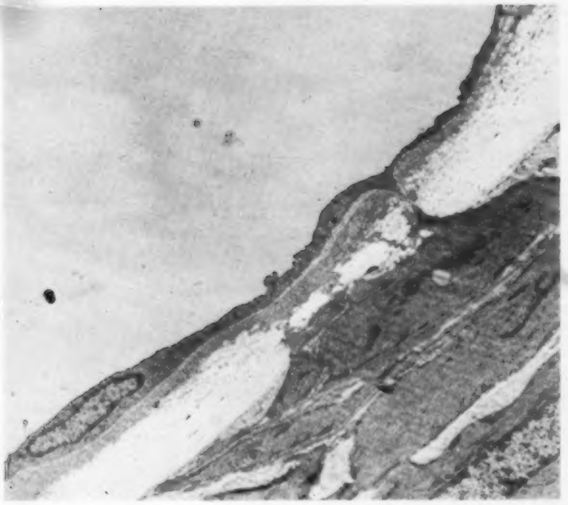


Figure 41: Arterial ultrastructure at E.M. Normal intima, no undulation. (L-lumen, E-endothelium, I-intima, IEL-internal elastic lamina, M-media).



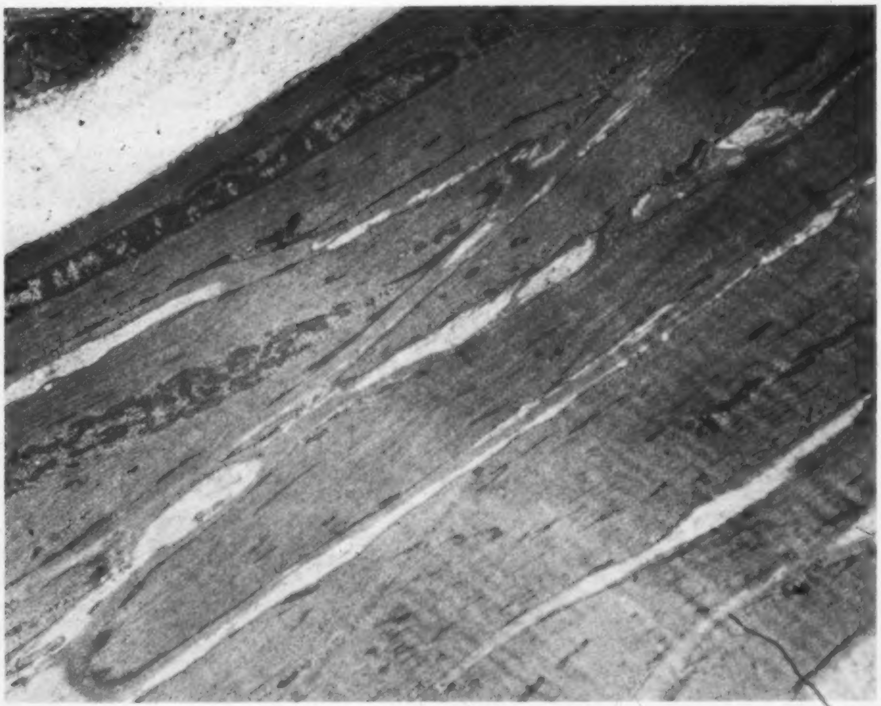


Figure 42: Arterial ultrastructure of the PPA (proximal pericallosal artery) for the 1.0 ml/kg SAH group at E.M.

(a) Minimal undulation of the intima

(b) Normal media musculature

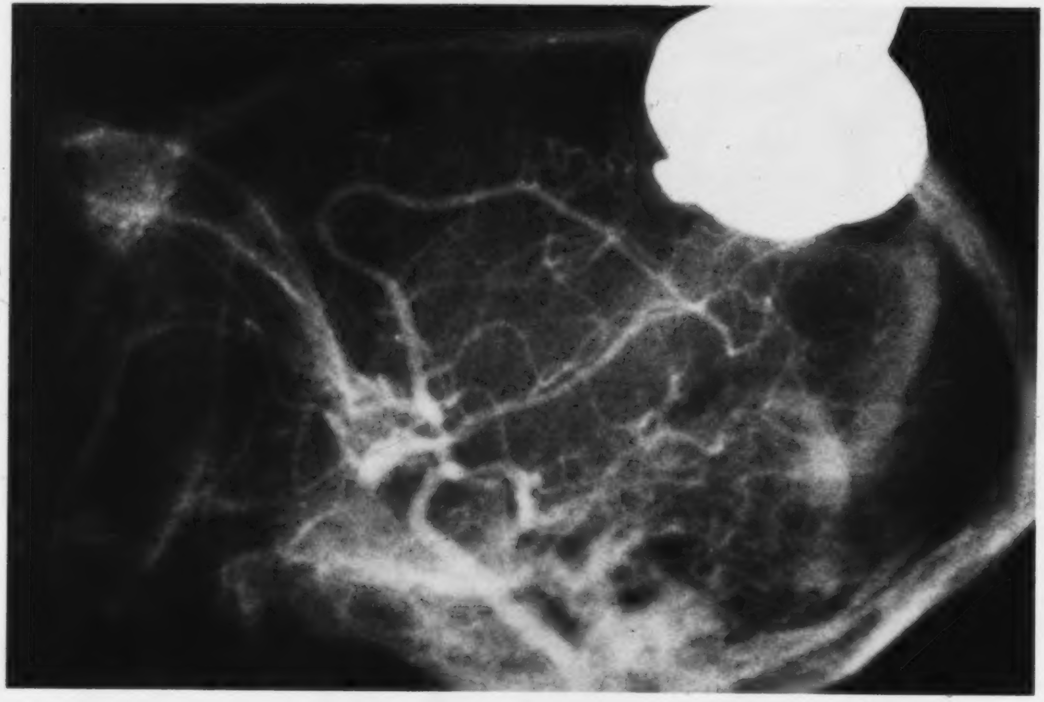


Figure 43 (a): Pre-SAH lateral cerebral angiogram for the 1.67 ml/kg group.

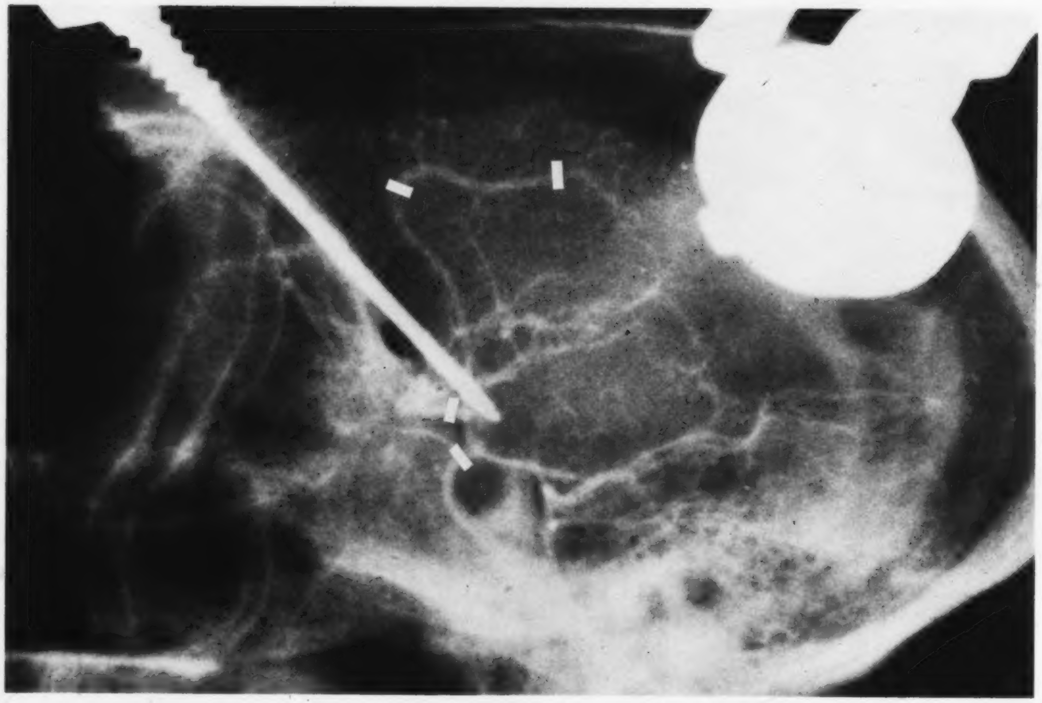


Figure 43 (b): Lateral cerebral angiogram for same animal as in Figure 43 (a) just prior to glutaraldehyde perfusion. Sites marked are areas at which the cerebral vessels were studied at E.M.

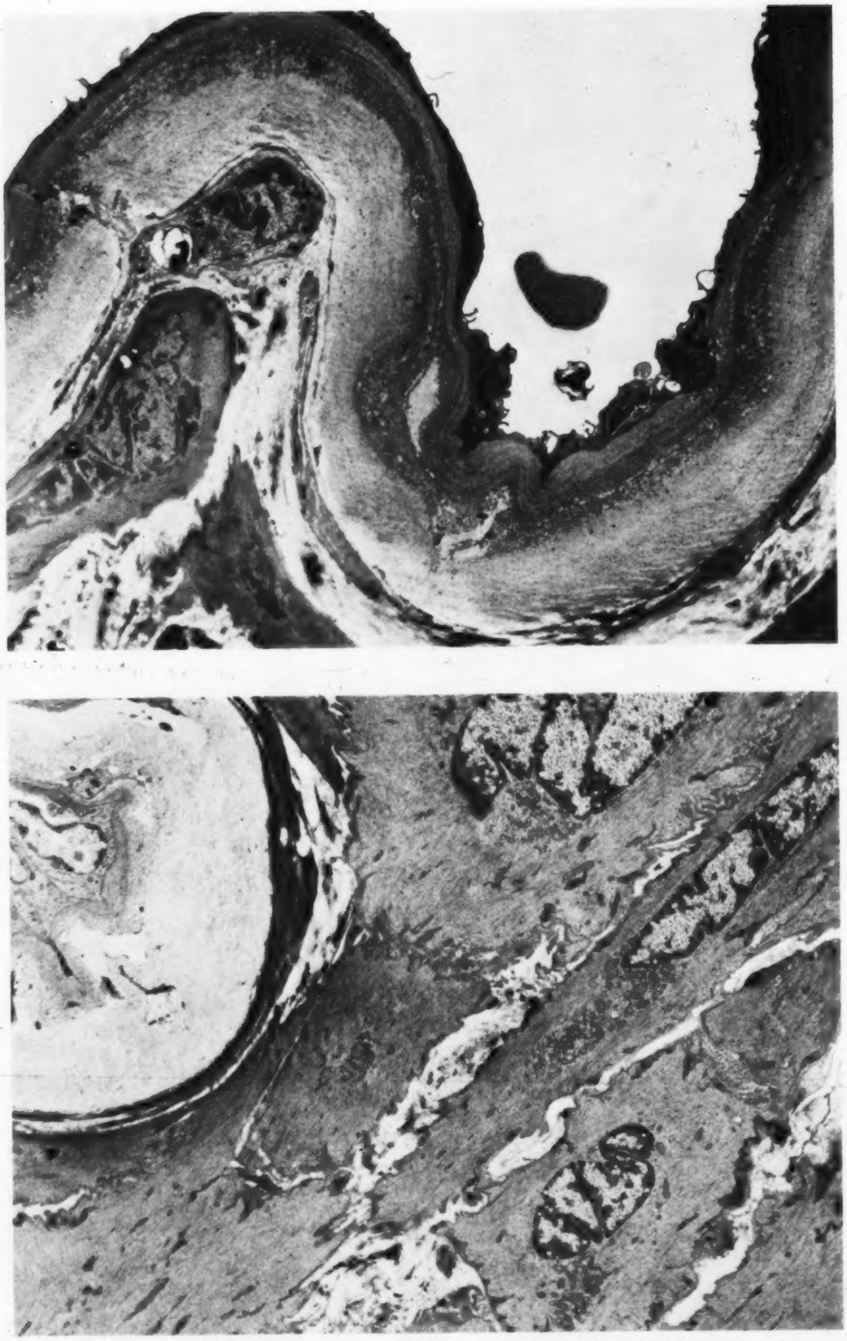


Figure 44: Arterial ultrastructure of the PPA (proximal pericallosal artery) for the 1.67 ml/kg SAH group at E.M. Same animal as in Figure 43.

(a) Marked intima undulation

(b) Marked contraction of the media musculature

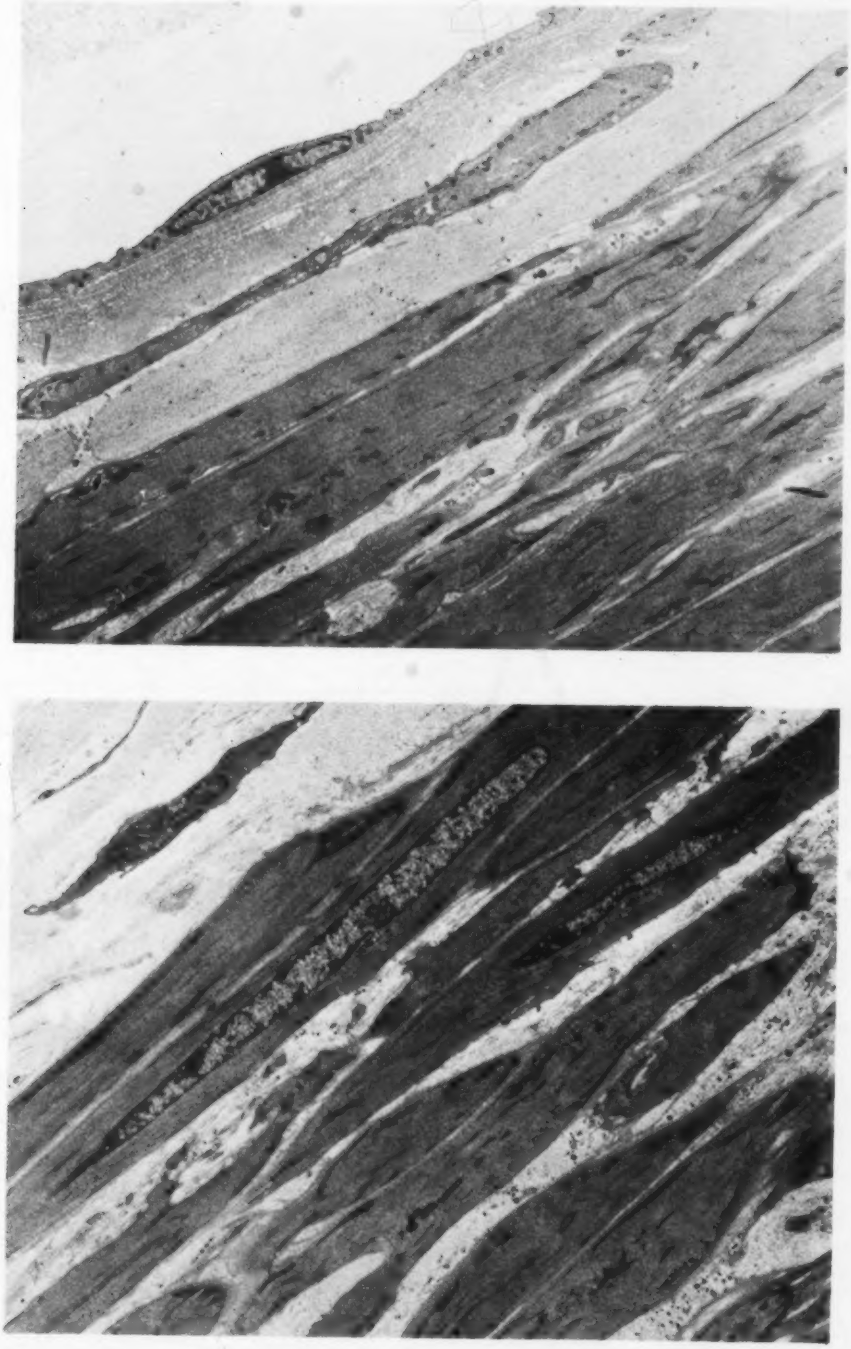


Figure 45: Arterial ultrastructure of the PPA (proximal pericallosal artery) for the 1.67 ml/kg SDH group at E.M.

(a) Minimal undulation of the intima

(b) Normal media musculature

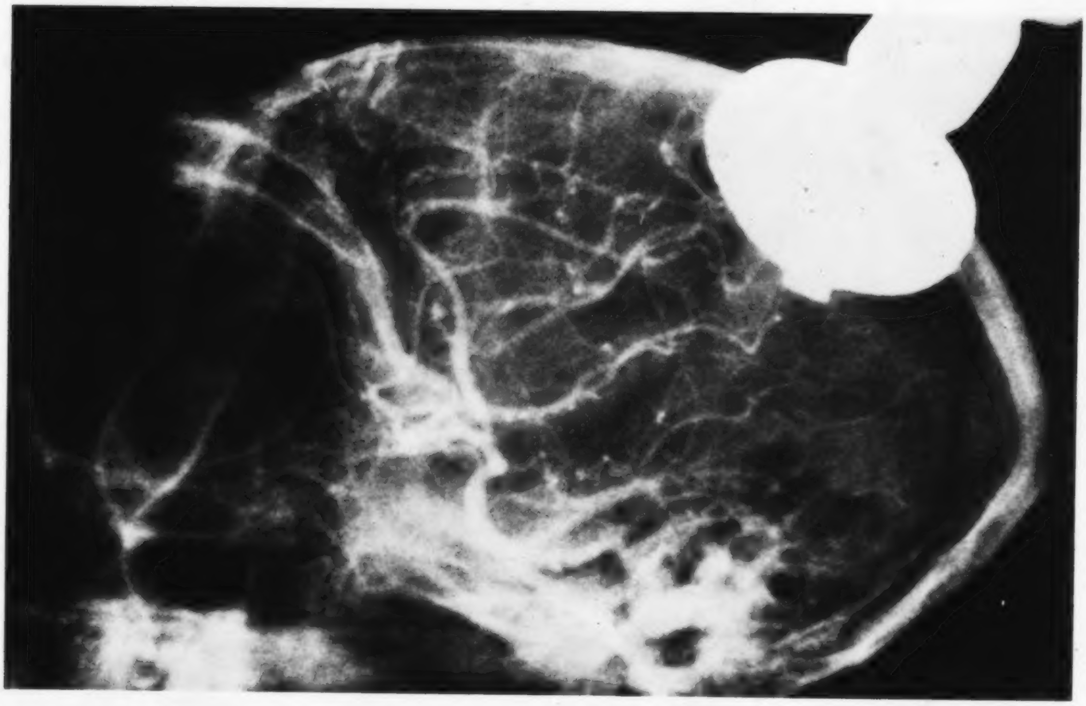


Figure 46 (a): Pre-insult lateral cerebral angiogram for the artificial CSF group.

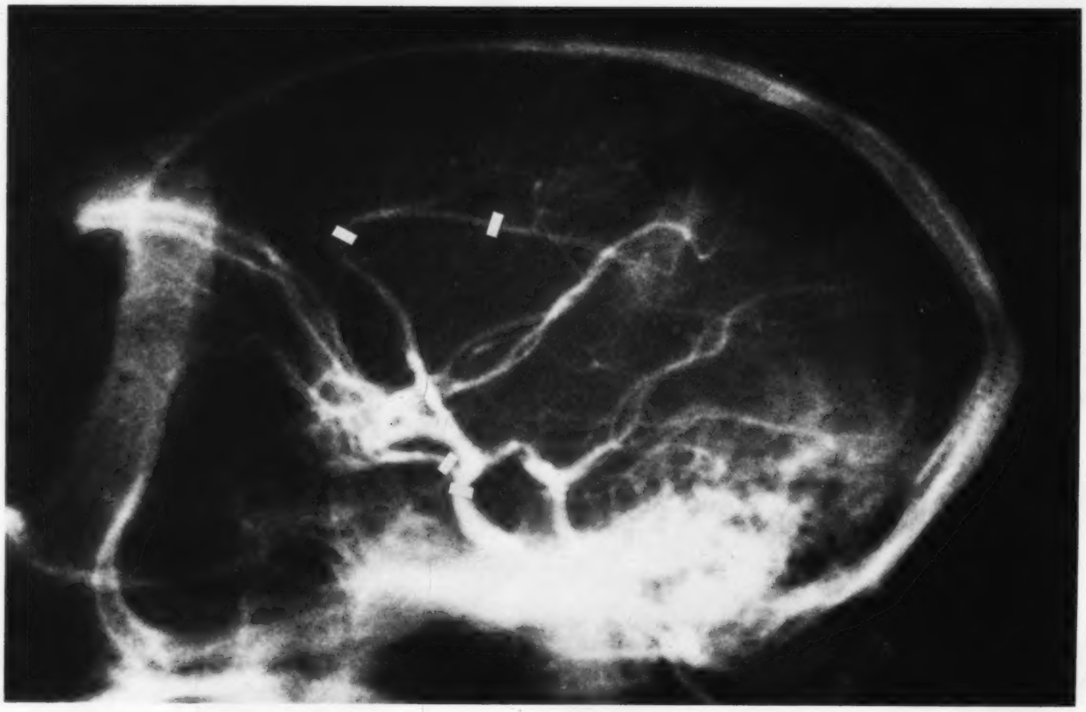


Figure 46 (b): Lateral cerebral angiogram for same animal as in Figure 46 (a) just prior to glutaraldehyde perfusion. Sites marked are areas at which the cerebral vessels were studied at E.M.

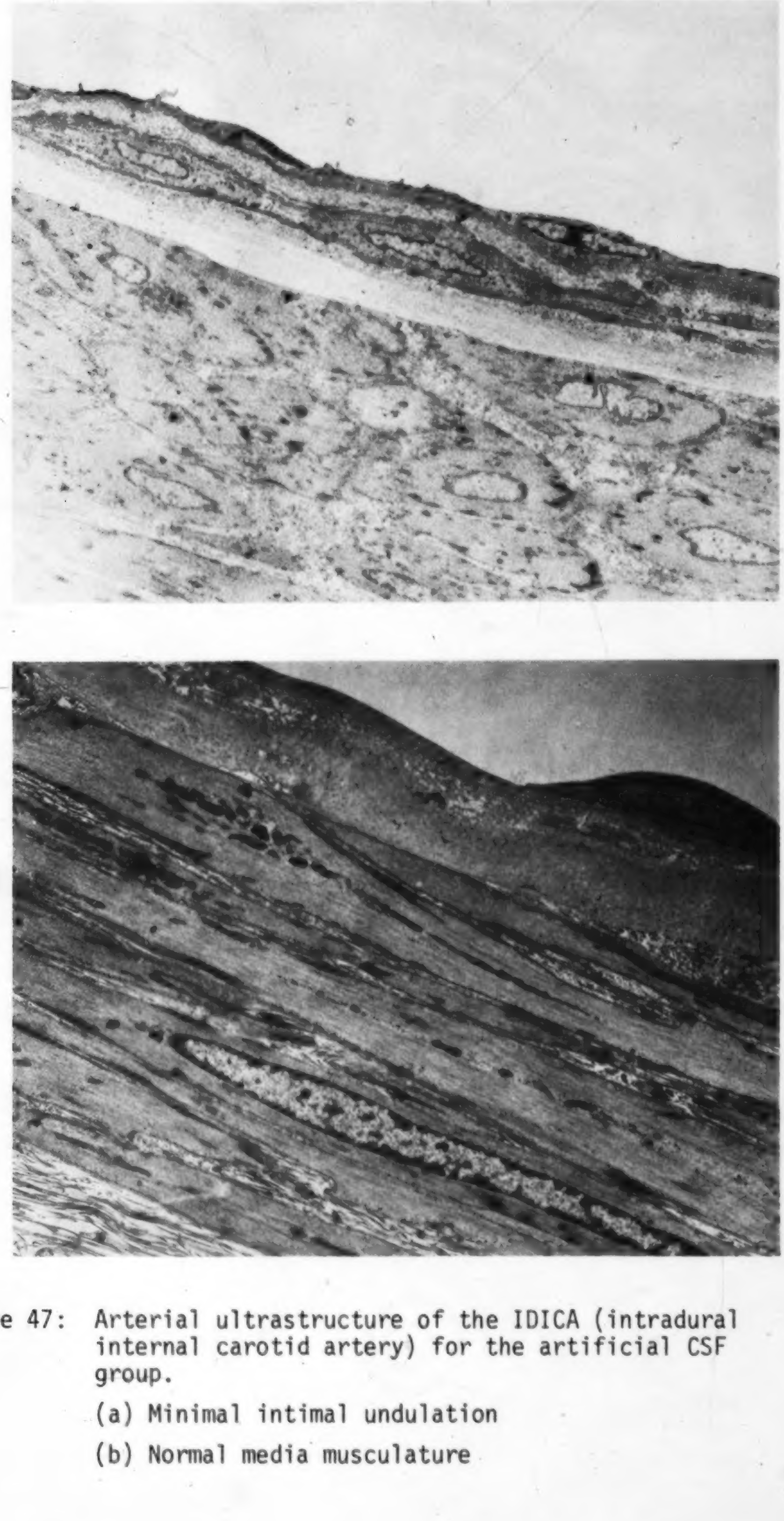


Figure 47: Arterial ultrastructure of the IDICA (intradural internal carotid artery) for the artificial CSF group.

(a) Minimal intimal undulation

(b) Normal media musculature

Figure 48: Histological section of pulmonary tissue from an animal in the artificial CSF group. Normal lung tissue.

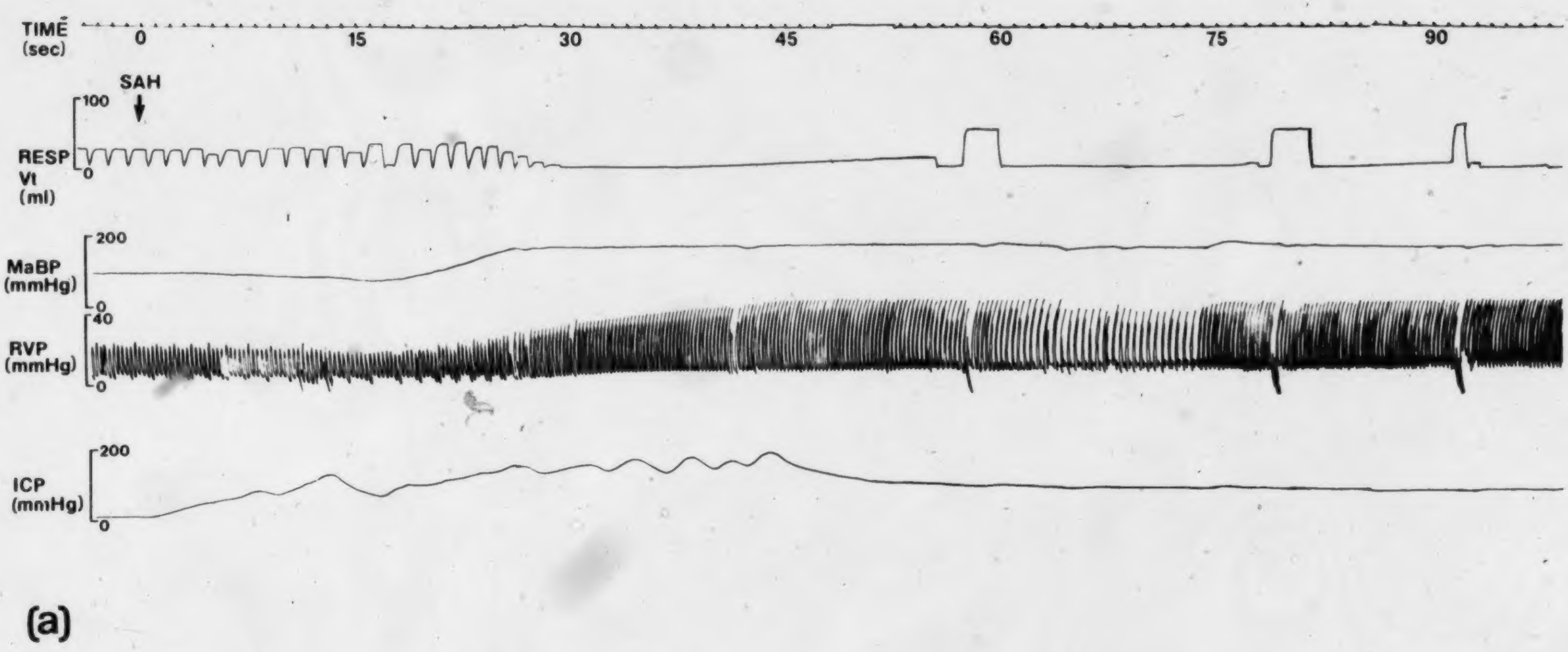


Figure 49 (a), (b): ICP, MaBP, respiratory pattern and RVP responses to an induced SAH. (continued)

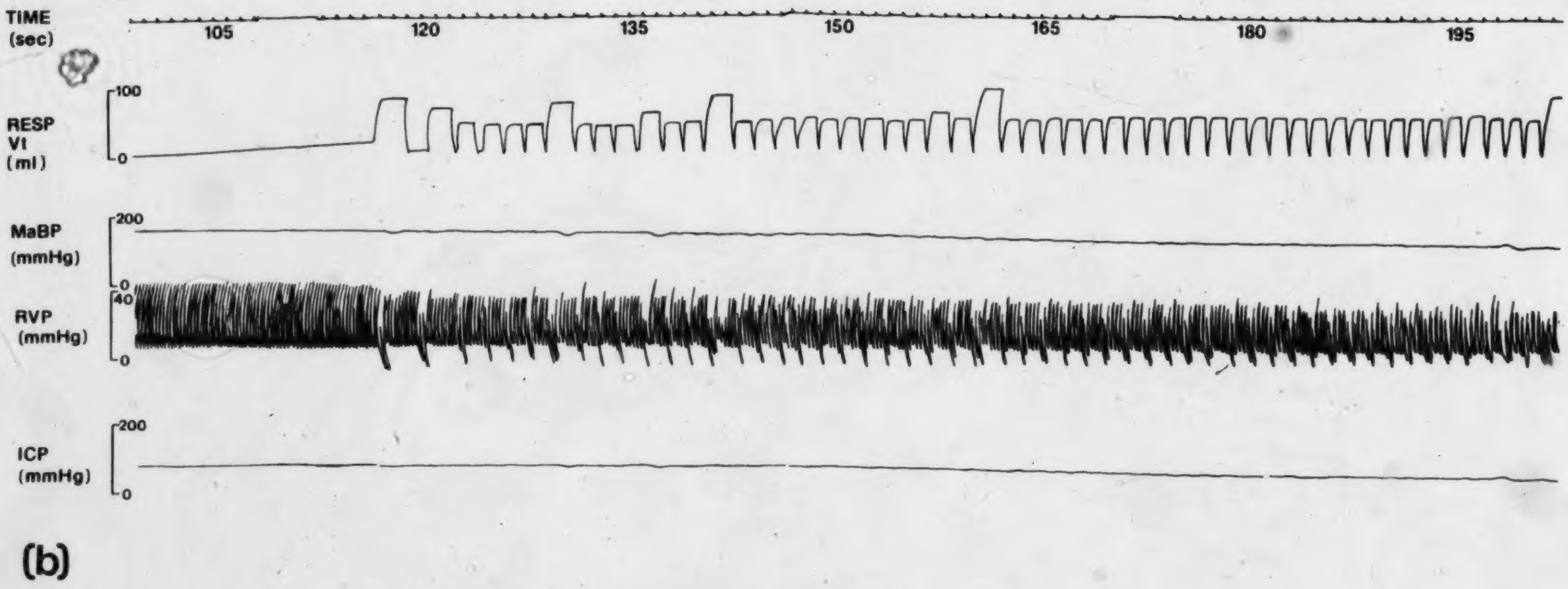


Figure 49(a), (b): ICP,MaBP,respiratory pattern and RVP responses to an induced SAH.

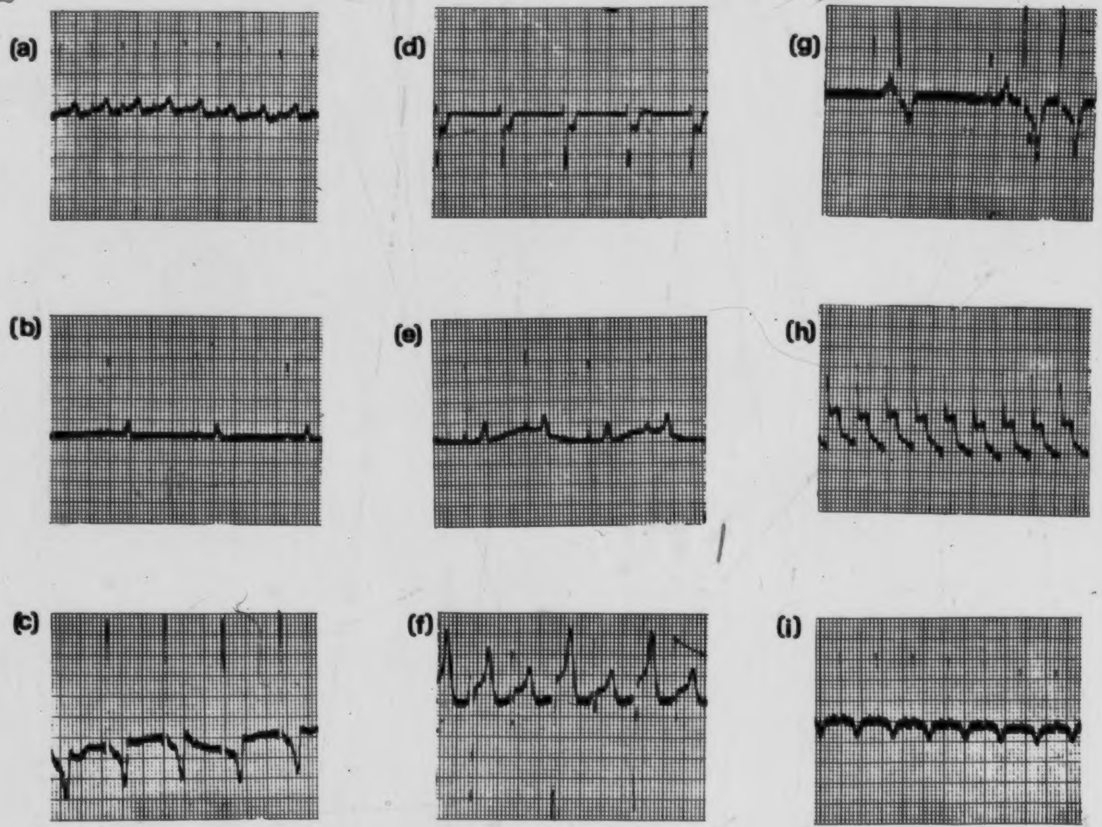


Figure 50: Cardiac rhythm and EKG pattern irregularities found following the various intracranial insults in this study. (a) Normal EKG; (b) Sinus bradycardia; (c) Idioventricular rhythm. (d) Complete A-V block; (e) Junctional rhythm;(f) Ventricular bigemini; (g)Premature ventricular contractions;(h) ST segment elevation; (i) T wave inversion.

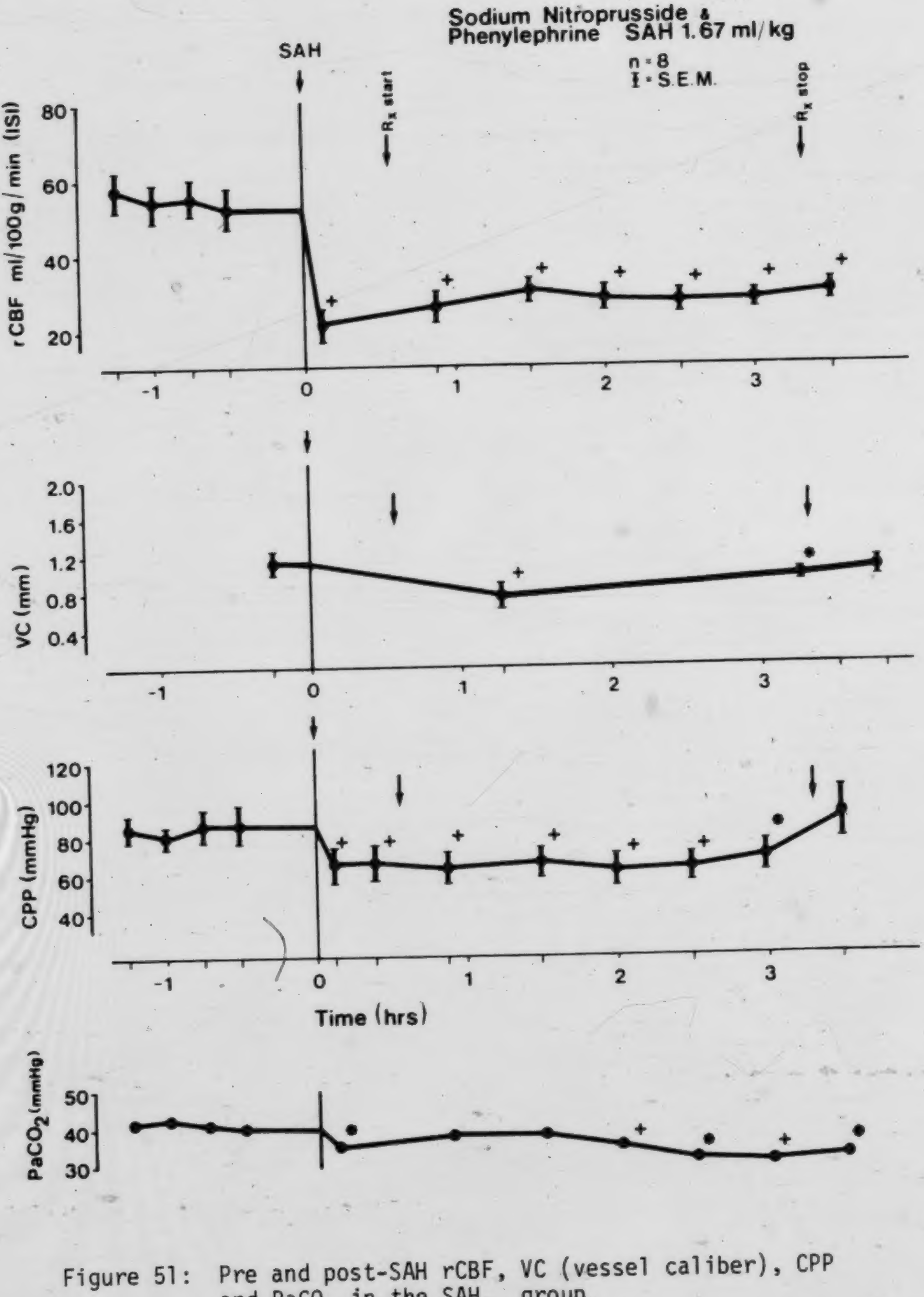


Figure 51: Pre and post-SAH rCBF, VC (vessel caliber), CPP and $PaCO_2$ in the SAH_{Rx} group.

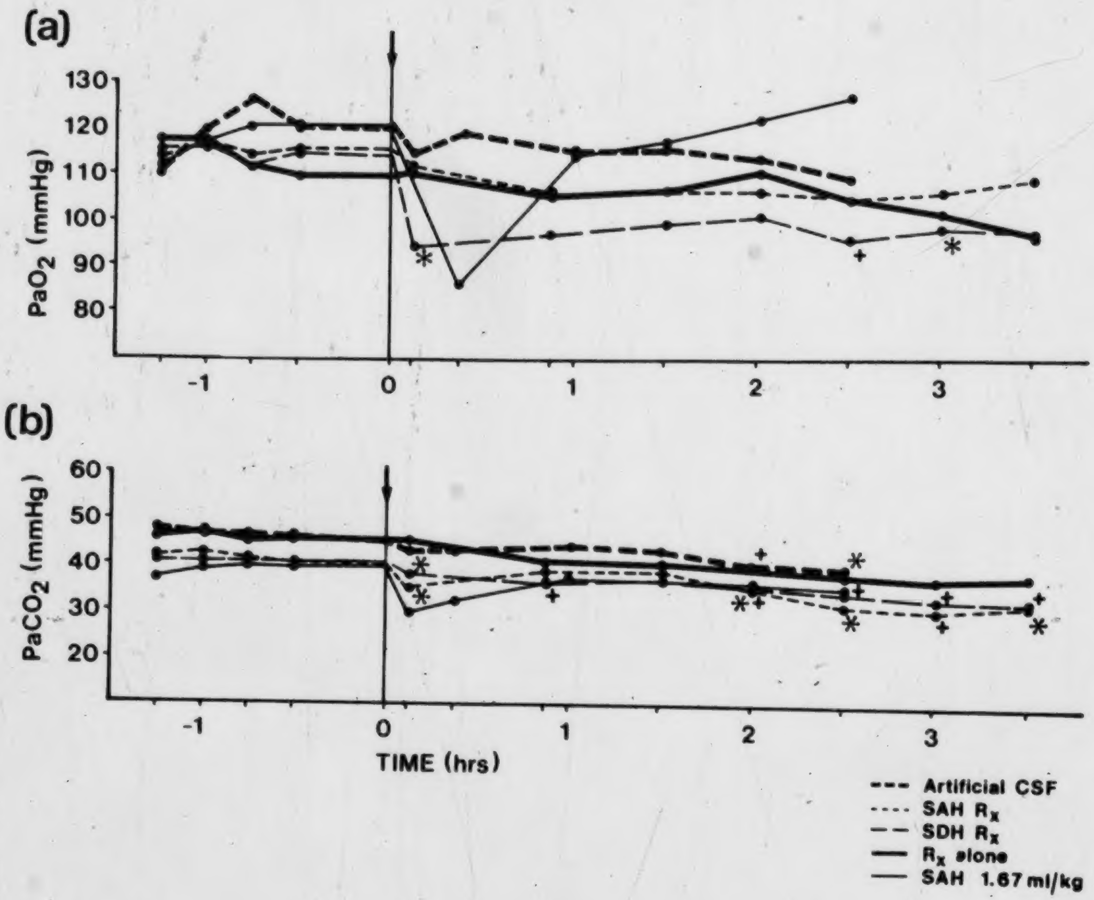


Figure 52: Pre and post-insult PaO$_2$ and PaCO$_2$ in the artifical CSF SAH$_{Rx}$, SDH$_{Rx}$, Rx alone and SAH 1.67 ml/kg groups.
(a) PaO$_2$
(b) PaCO$_2$

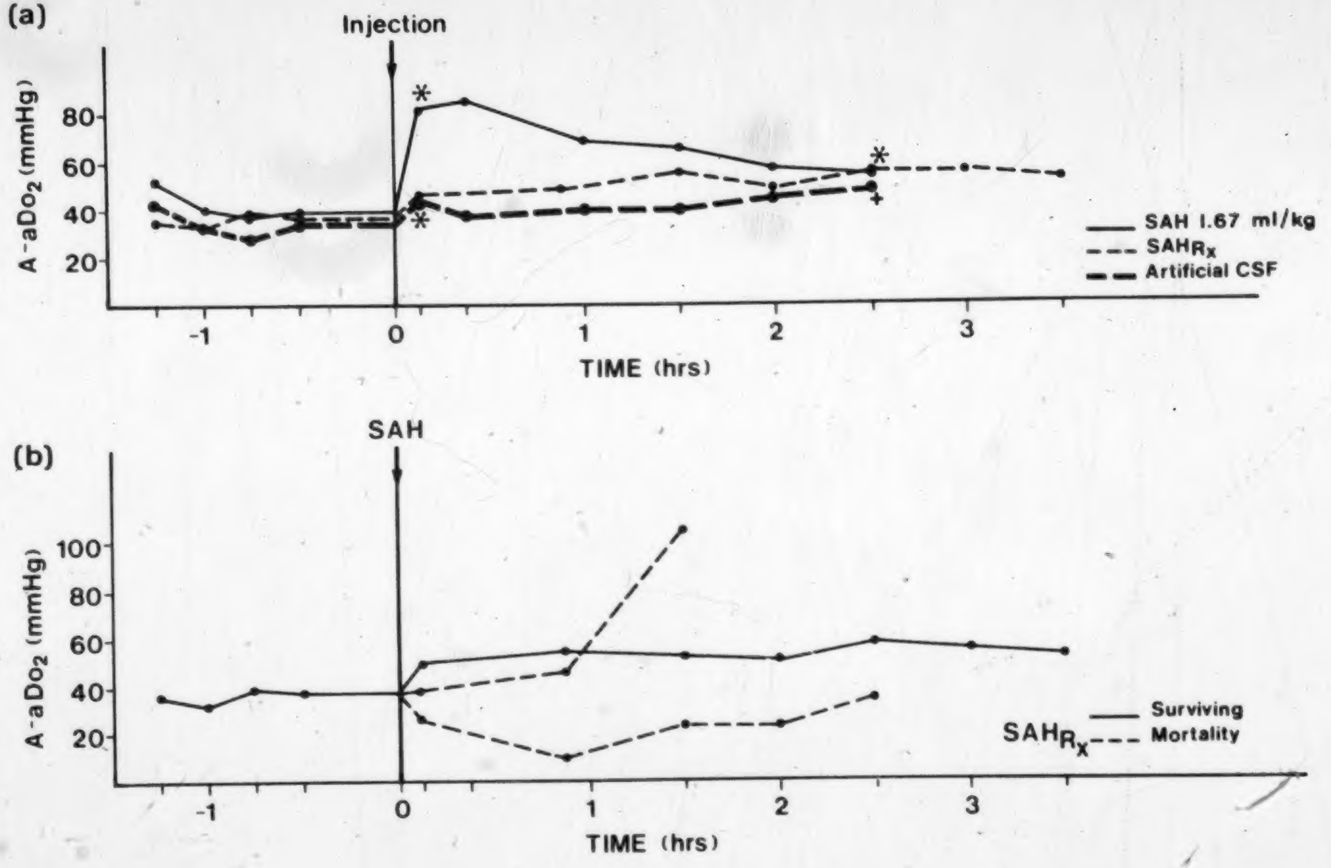


Figure 53 (a): Pre and post-insult A-aDO$_2$ for all animals in the SAH 1.67 ml/kg, SAH$_{Rx}$ and artificial CSF groups.

(b): Post SAH A-aDO$_2$ for those animals surviving the 5 hour observation period and those dying within this time.

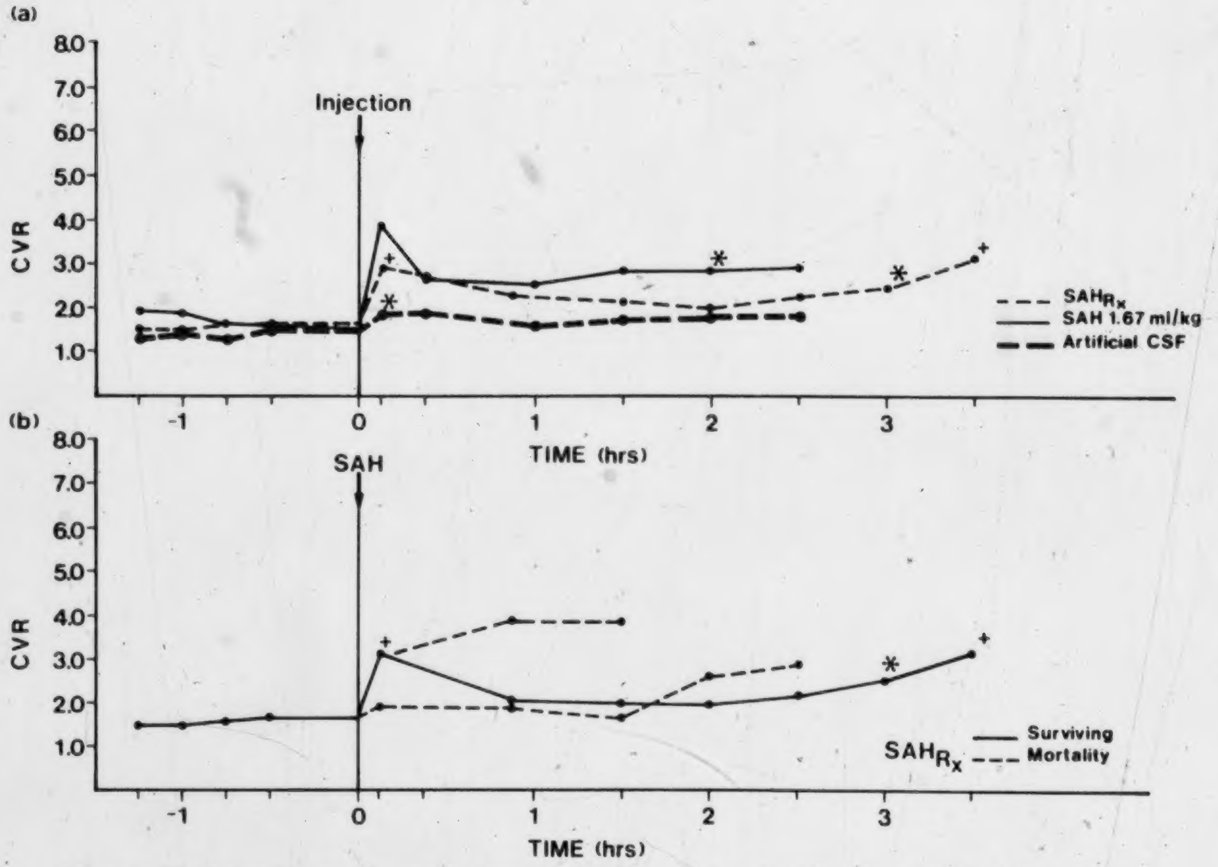


Figure 54 (a): Pre and post-insult CVR for all animals surviving the 5 hour observation period in the SAH$_{Rx}$, SAH 1.67 ml/kg and artificial CSF groups.

(b): Post-SAH CVR for those animals surviving the 5 hour observation period and those dying within this period for the SAH$_{Rx}$ group.

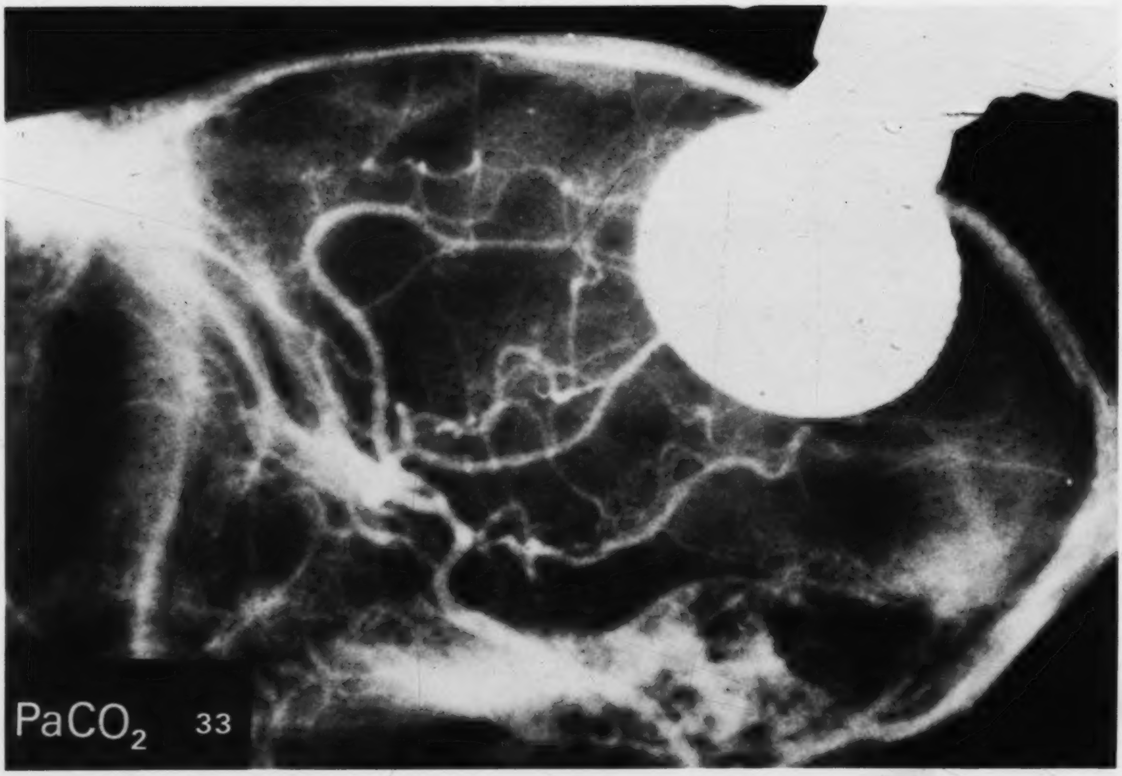


Figure 55 (a): Pre-SAH lateral cerebral angiogram for the SAH_{Rx} group.

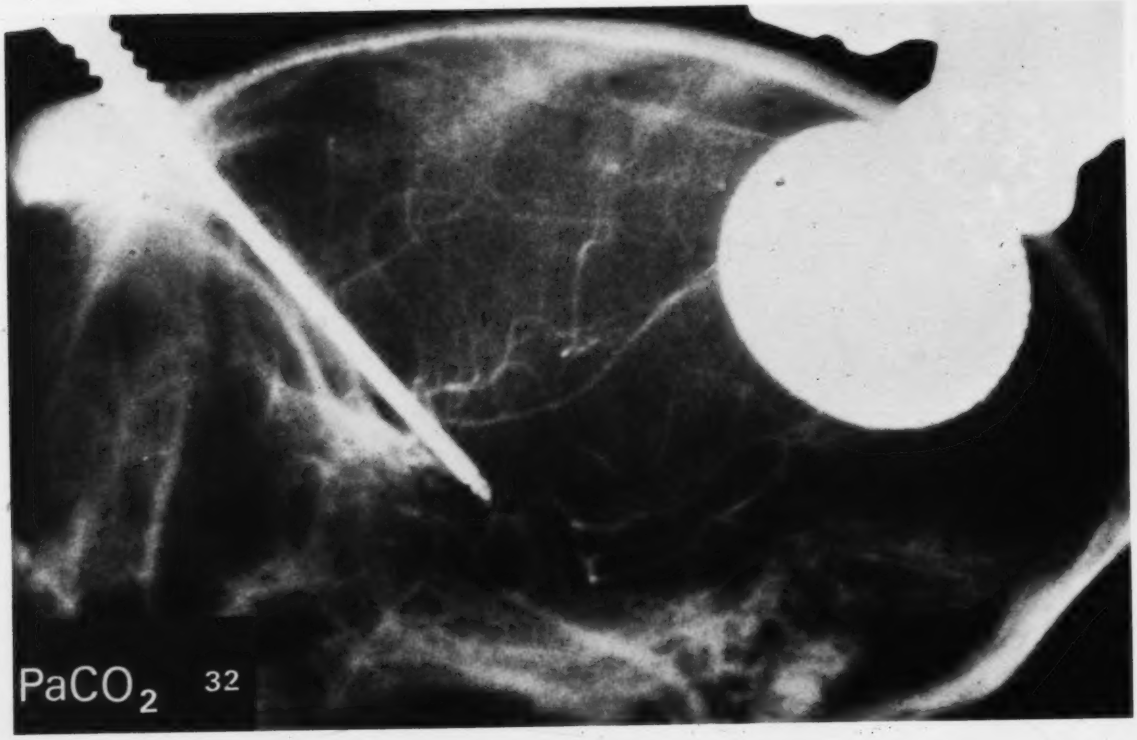


Figure 55 (b): Post-SAH (65 minutes) lateral cerebral angiogram for the SAH_{Rx} group.

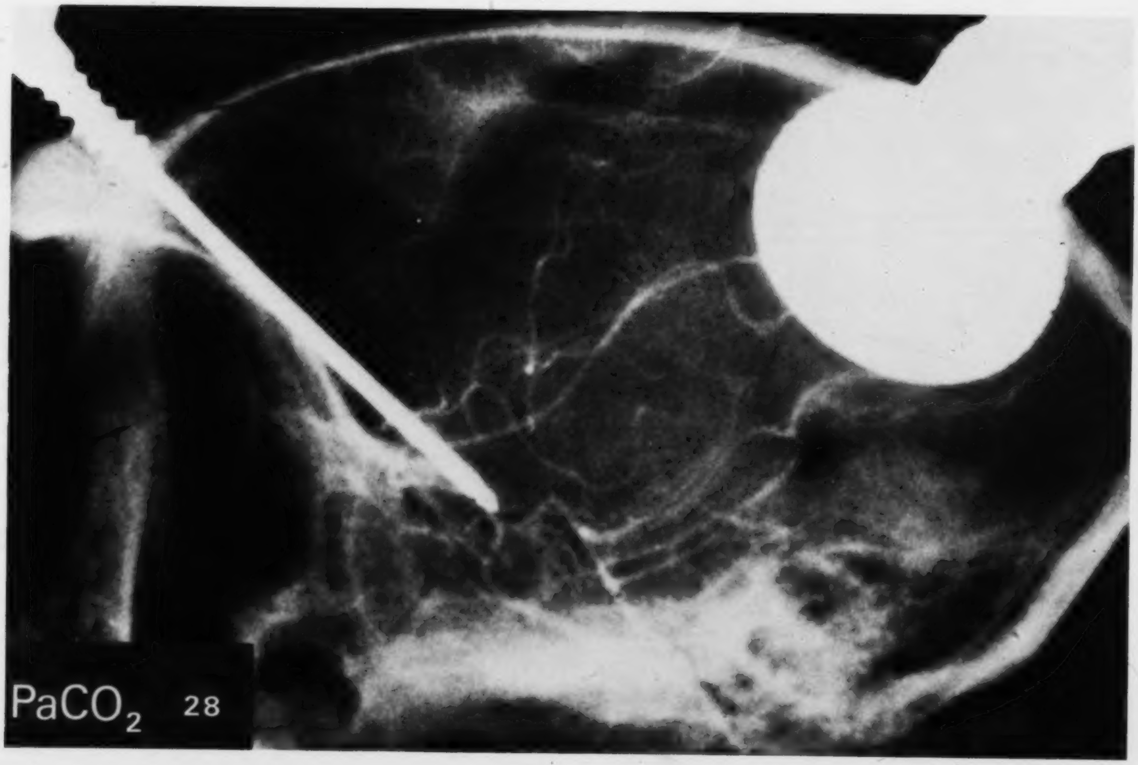


Figure 55 (c): Post-SAH (207 minutes) lateral cerebral angiogram for the SAH_{Rx} group.

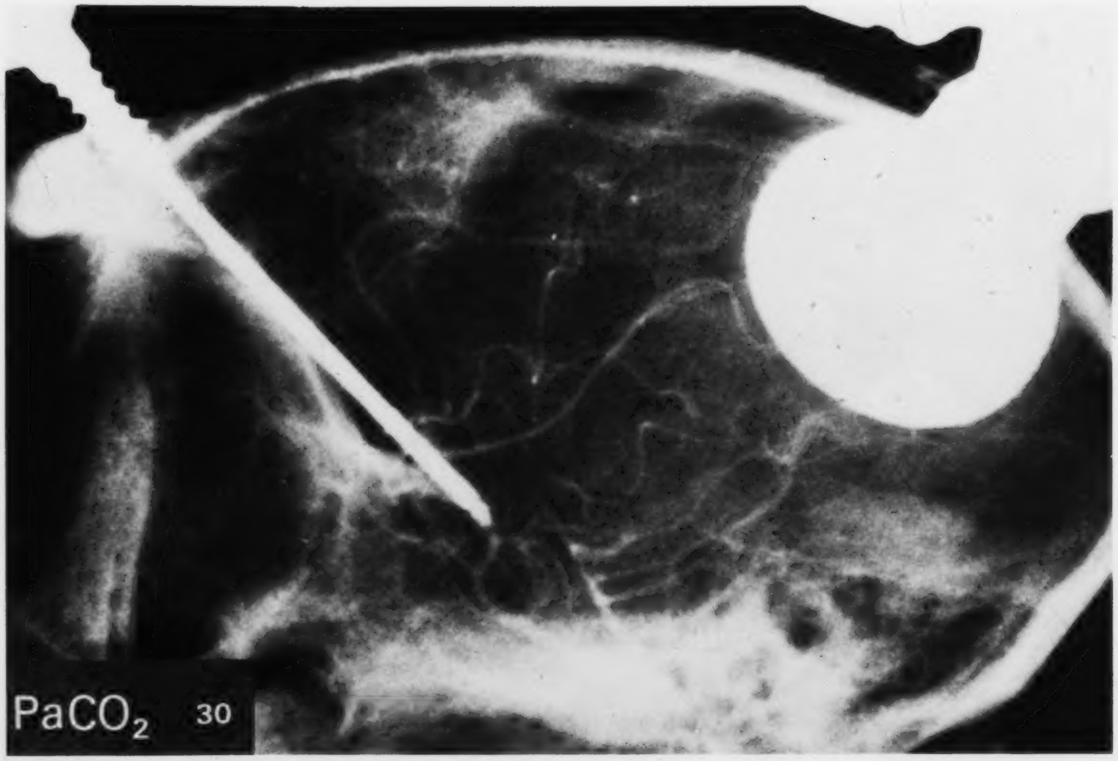


Figure 55 (d): Post-SAH (242 minutes) lateral cerebral angiogram for the SAH_{Rx} group.

Figure 56: Histological section of pulmonary tissue from an animal in the SAH$_{Rx}$ group demonstrating moderate intra-alveolar and interstitial edema.

Figure 57: Histological section of pulmonary tissue from an animal in the SAHRx group that died immediately following the insult demonstrating moderate hemorrhagic intra-alveolar edema.

Figure 58: Histological section of pulmonary tissue from an animal in the intracerebral hemorrhage group demonstrating moderate intra-alveolar edema.

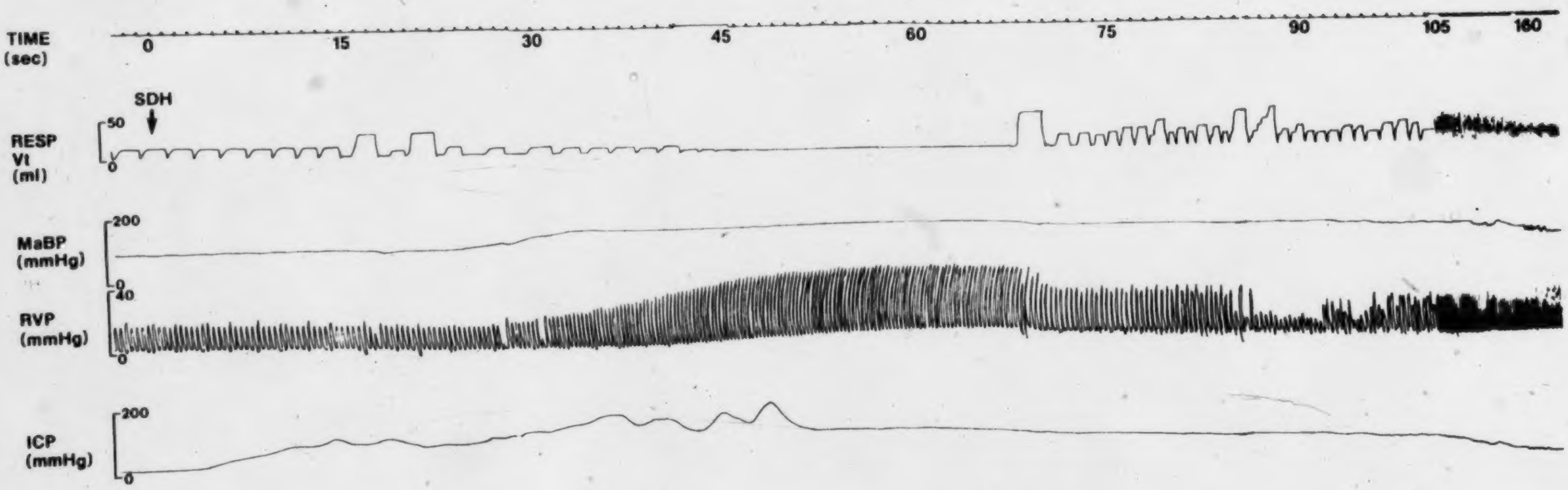


Figure 59: ICP, MaBP, respiratory pattern and RVP responses to induced SDH in the SDH_{Rx} group.

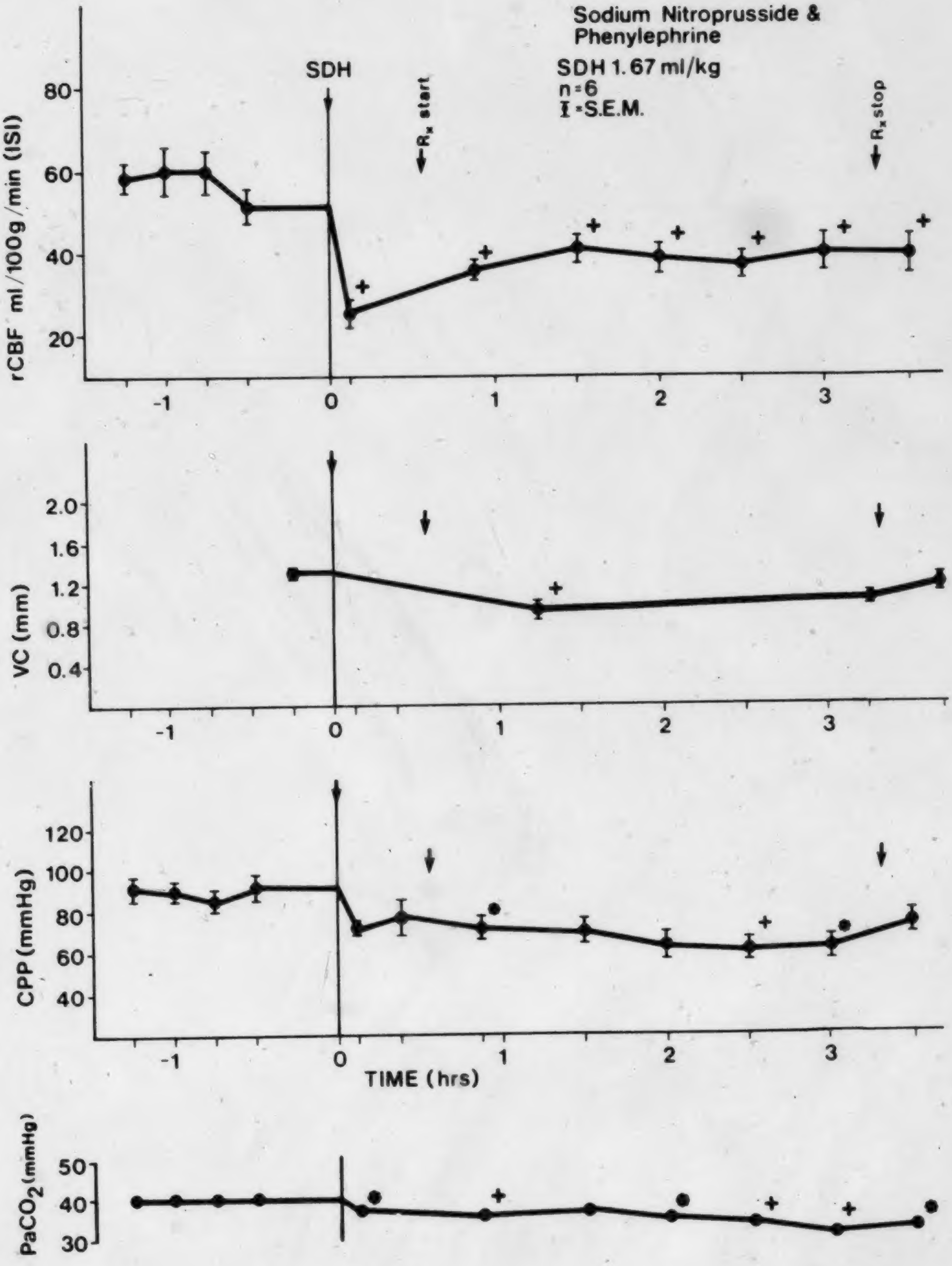


Figure 60: Pre and post-SAH rCBF, VC (vessel caliber), CPP and $PaCO_2$ in the SDH_{Rx} group.

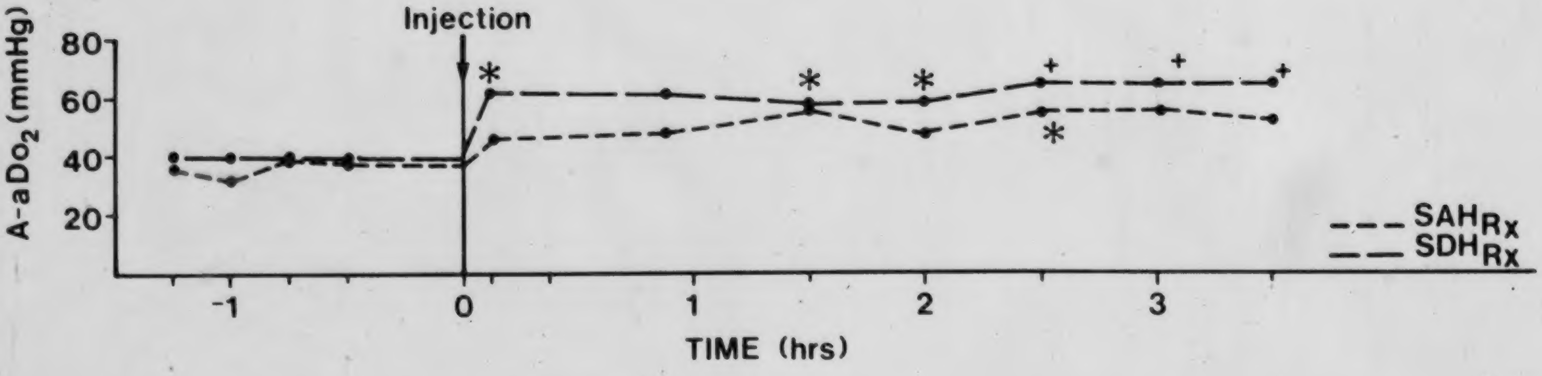


Figure 61: Pre and post-insult A-aDO$_2$ in the SAH$_{Rx}$ and SDH$_{Rx}$ groups.

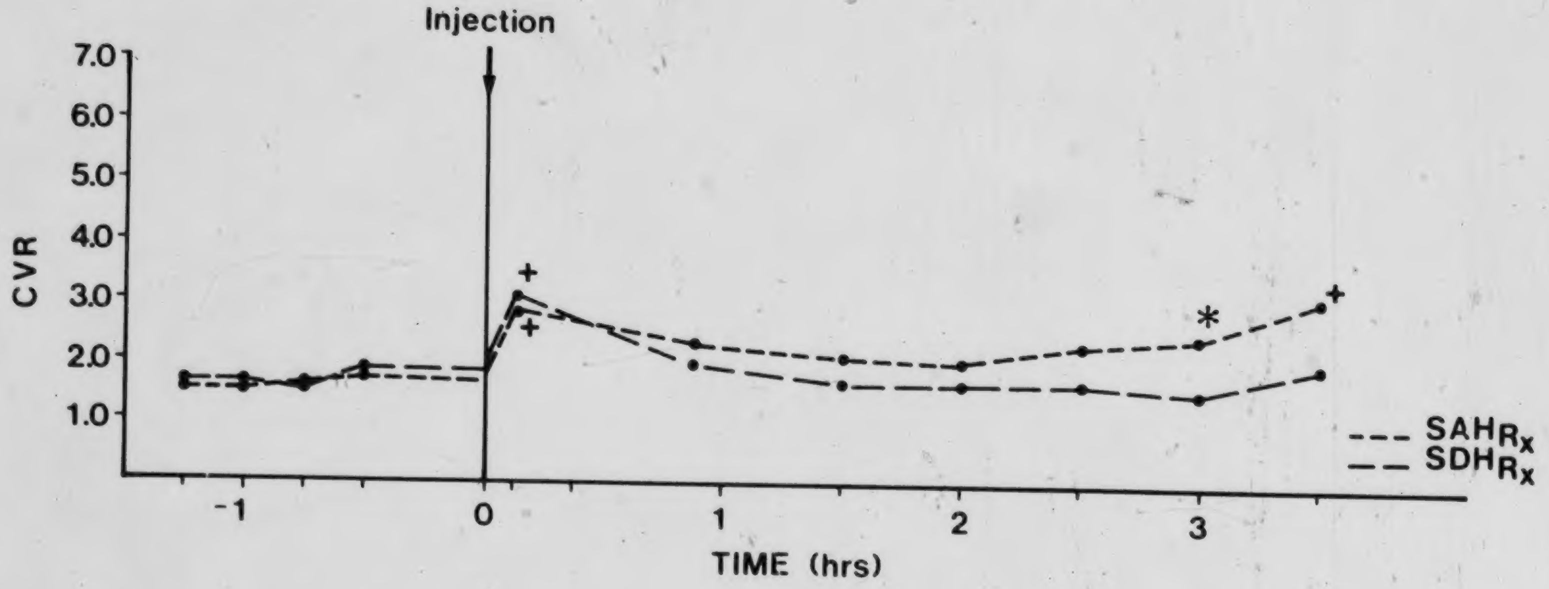


Figure 62: Pre and post-insult CVR in the SAH_{Rx} and SDH_{Rx} groups.

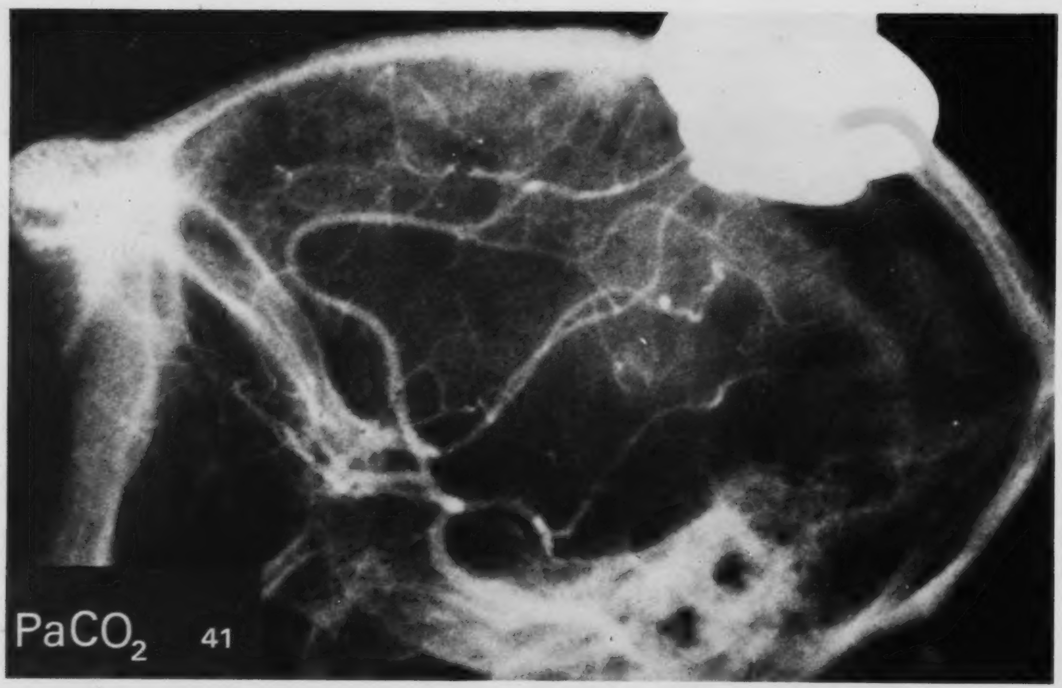


Figure 63 (a): Pre-SDH lateral cerebral angiogram for the SDH Rx group.

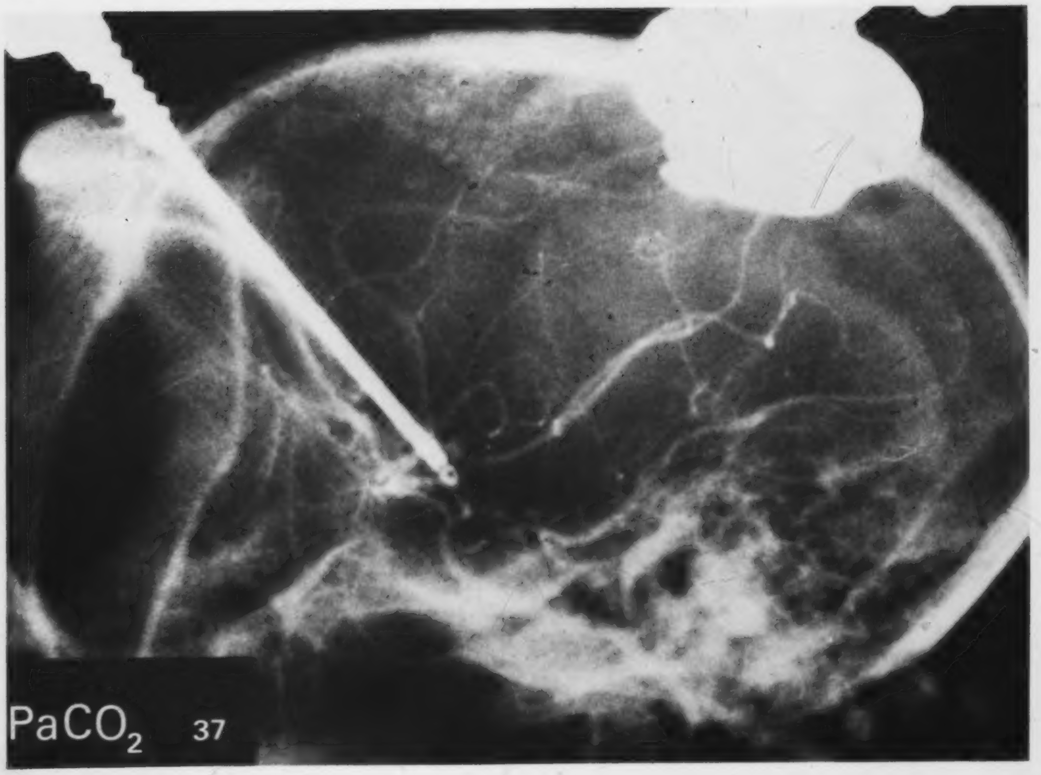


Figure 63 (b): Post-SDH (77 minutes) lateral cerebral angiogram for the SDH Rx group.

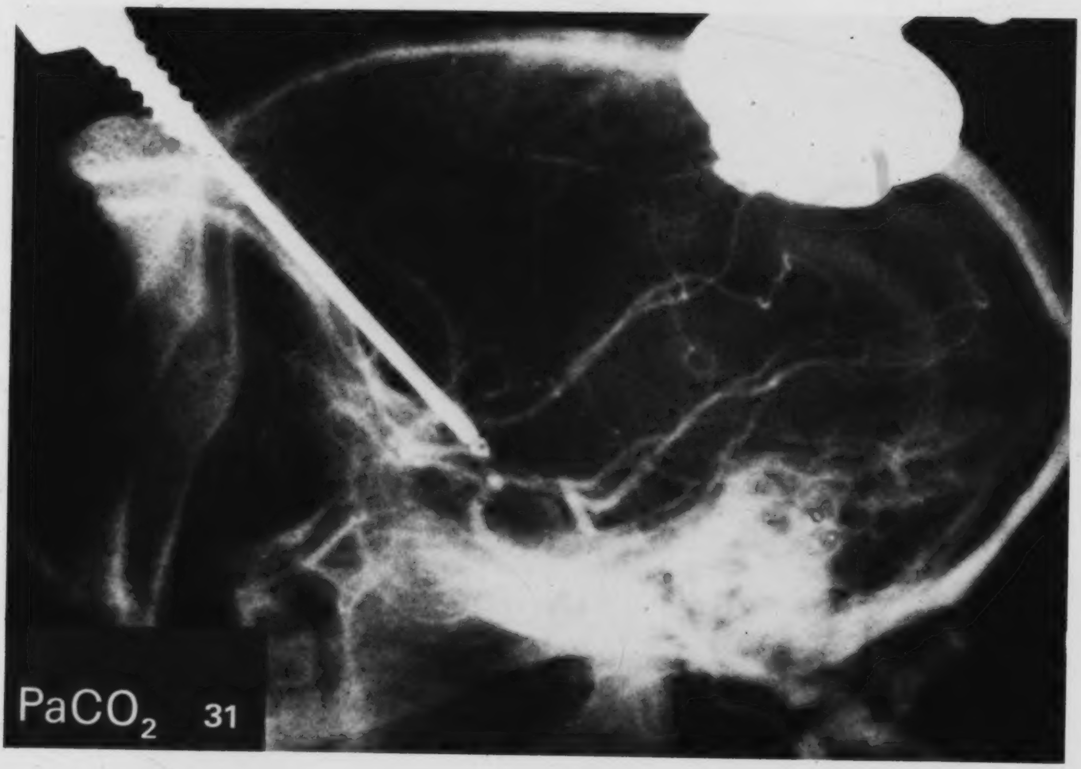


Figure 63 (c): Post-SDH (219 minutes) lateral cerebral angiogram for the SDH Rx group.

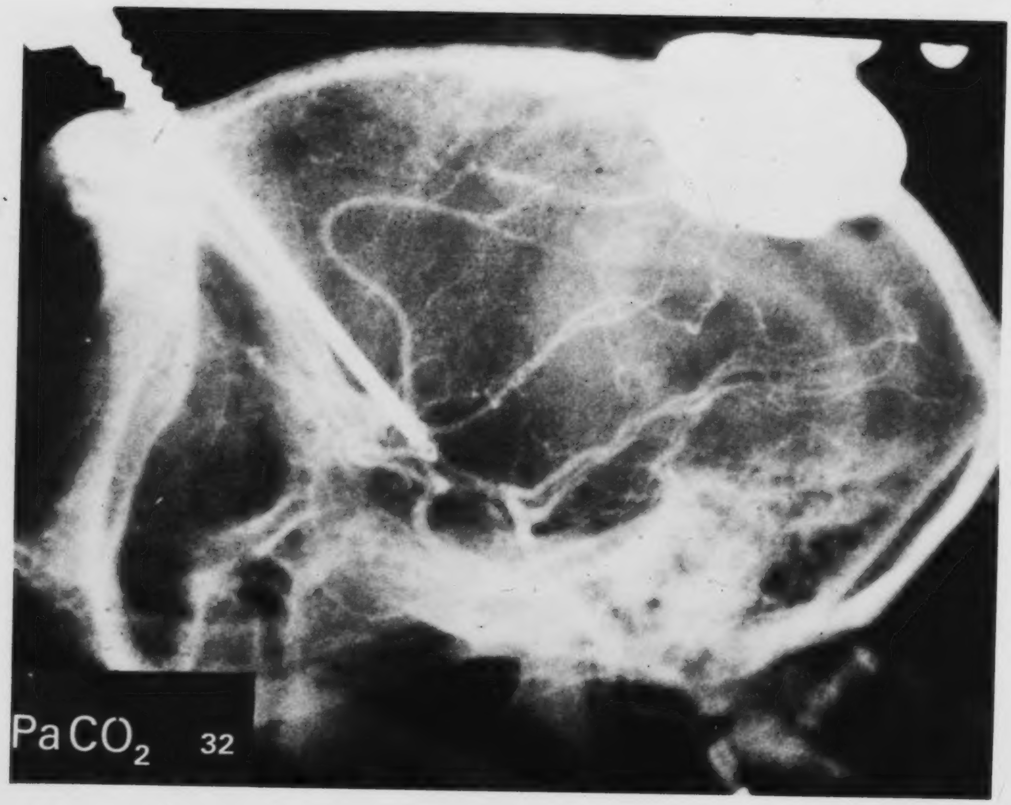


Figure 63 (d): Post-SDH (258 minutes) lateral cerebral angiogram for the SDH Rx group.

Figure 64: Histological section of pulmonary tissue from an animal in the SDHRx group demonstrating moderate interstitial edema.

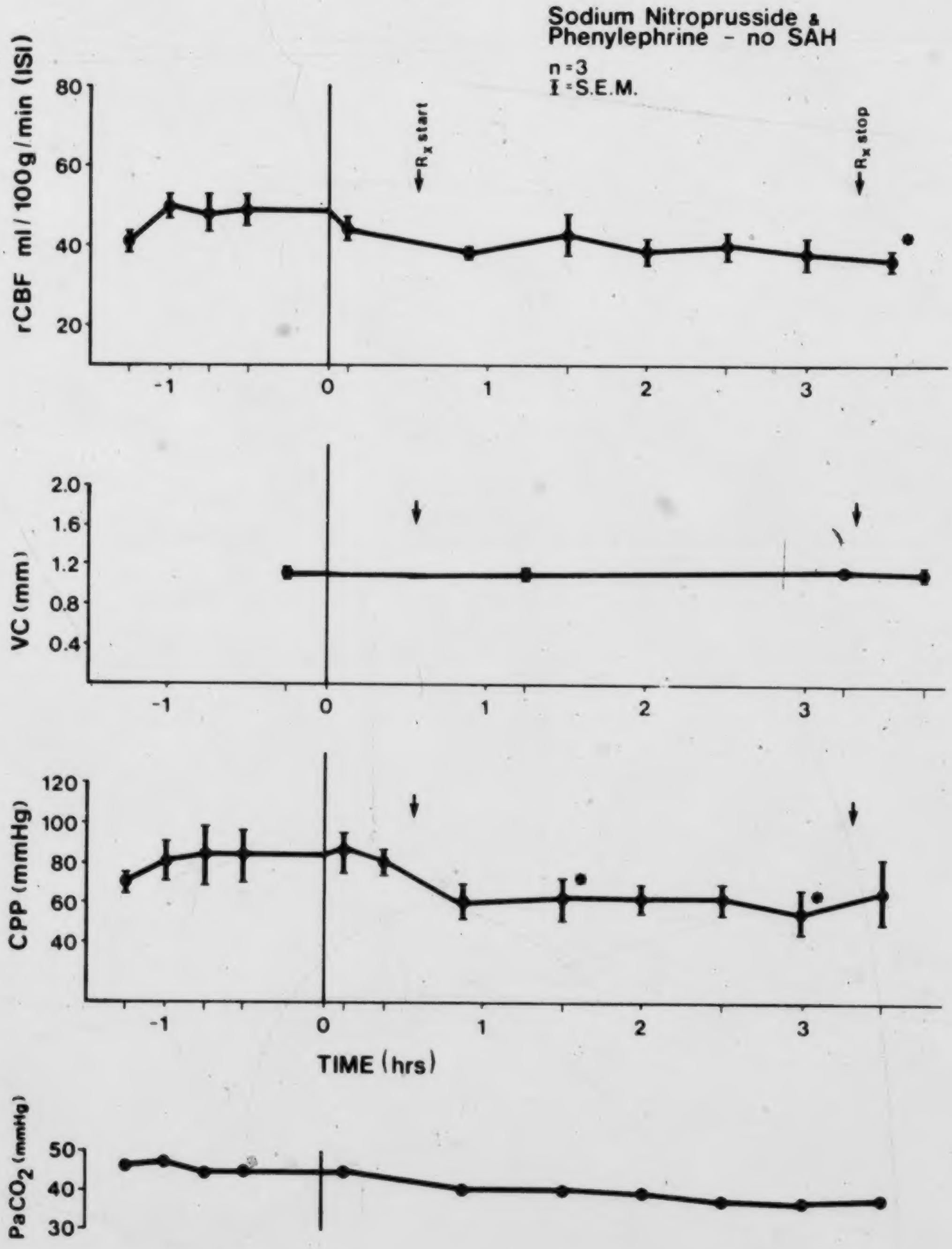


Figure 65: Pre and post-hypothetical insult rCBF, VC (vessel caliber), CPP and $PaCO_2$ for the Rx alone group.

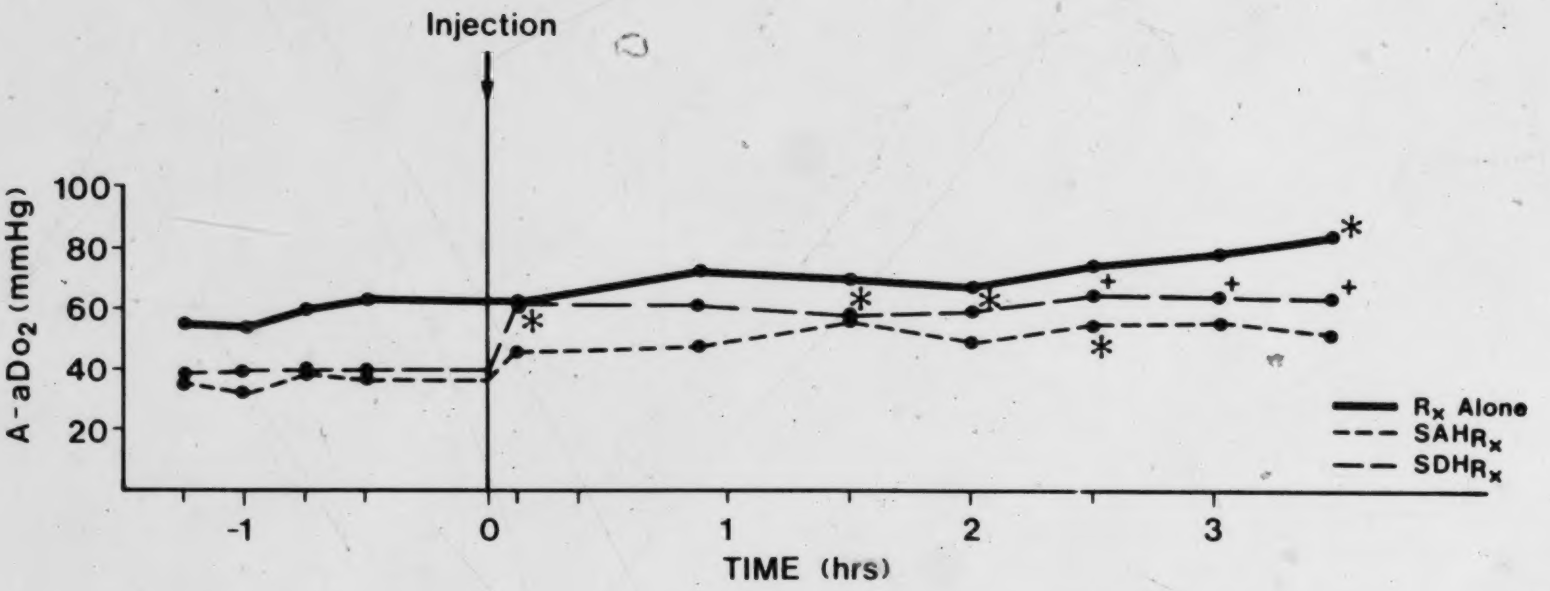


Figure 66: Pre and post-insult A-aDO$_2$ for the Rx alone (hypothetical insult), SAH$_{Rx}$ and SDH$_{Rx}$ groups.

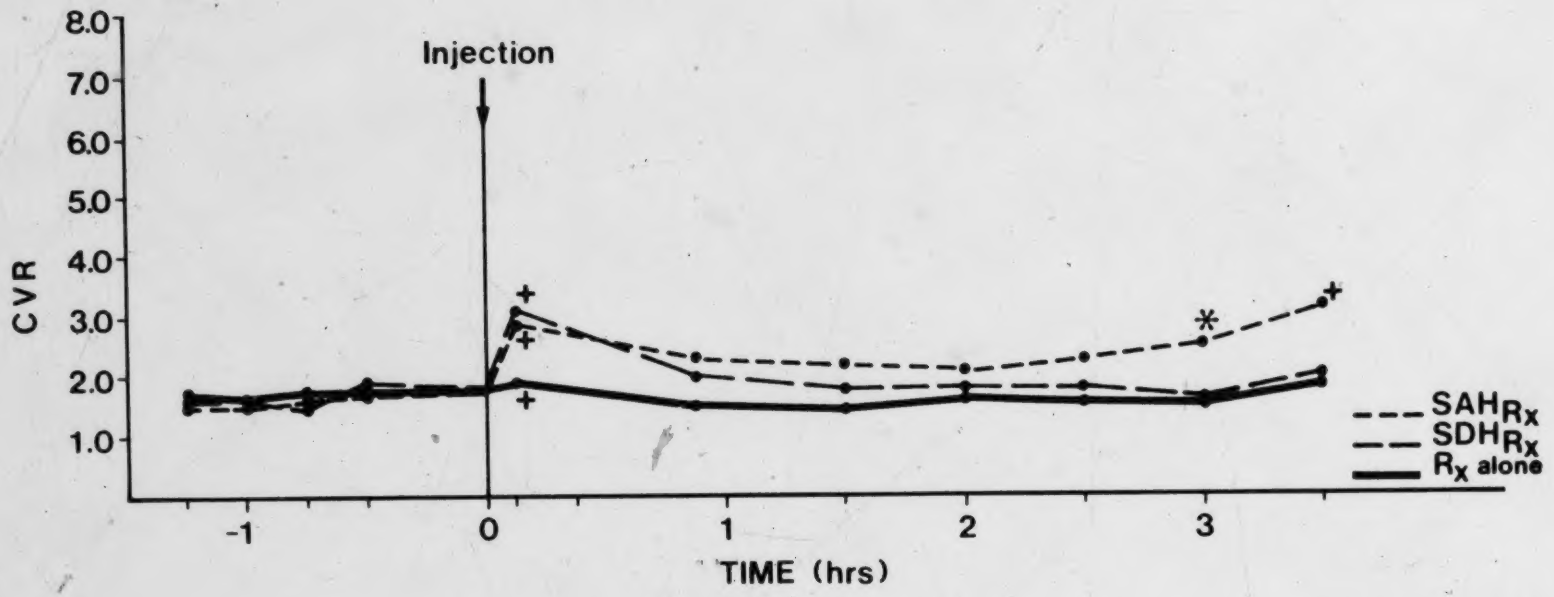


Figure 67: Pre and post-insult CVR for the SAH$_{Rx}$, SDH$_{Rx}$, and Rx alone (hypothetical insult) groups.

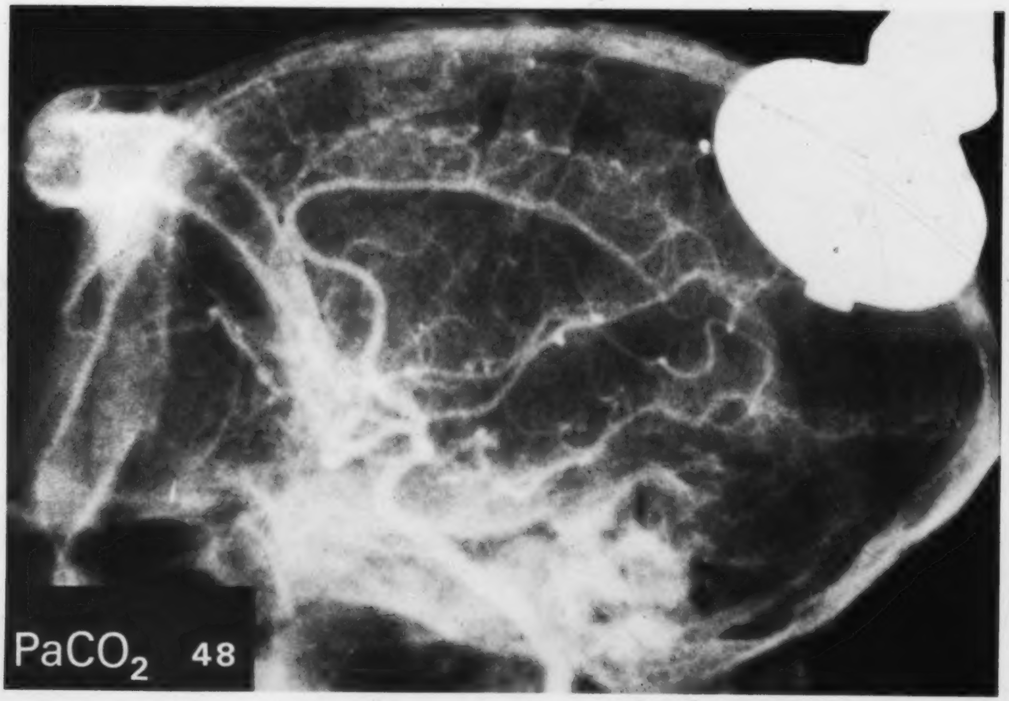


Figure 68 (a): Pre-hypothetical insult lateral cerebral angiogram for the Rx alone group.

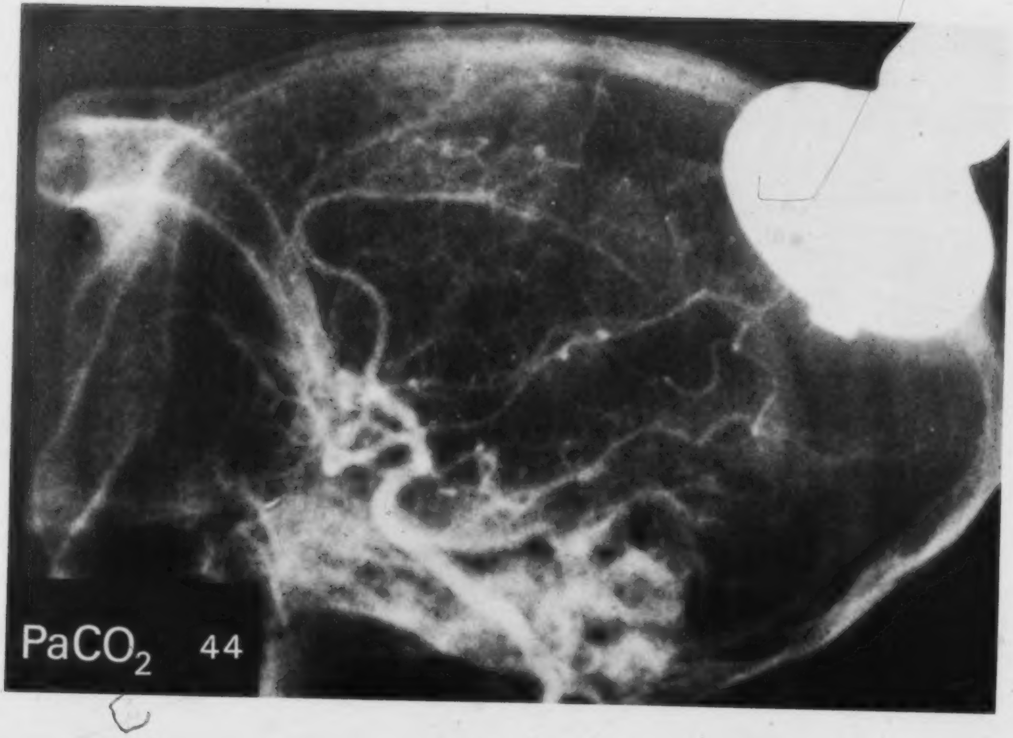


Figure 68 (b): Post-hypothetical (75 minutes) lateral cerebral angiogram for the Rx alone group.

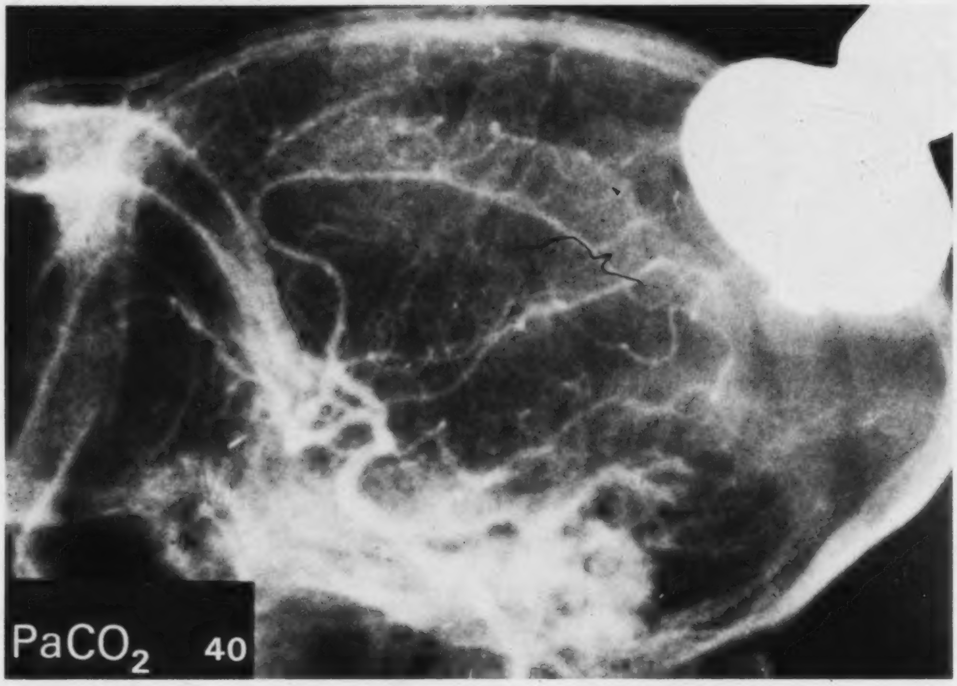


Figure 68 (c): Post-hypothetical (215 minutes) lateral cerebral angiogram for the Rx alone group.

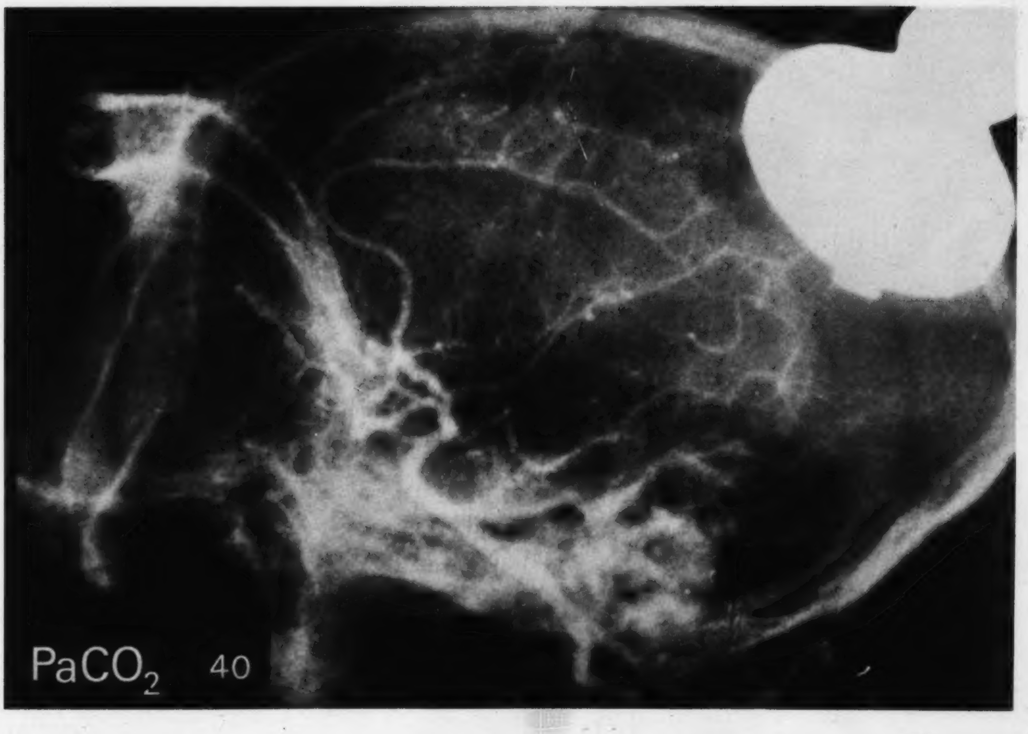


Figure 68 (d): Post-hypothetical (260 minutes) lateral cerebral angiogram for the Rx alone group.

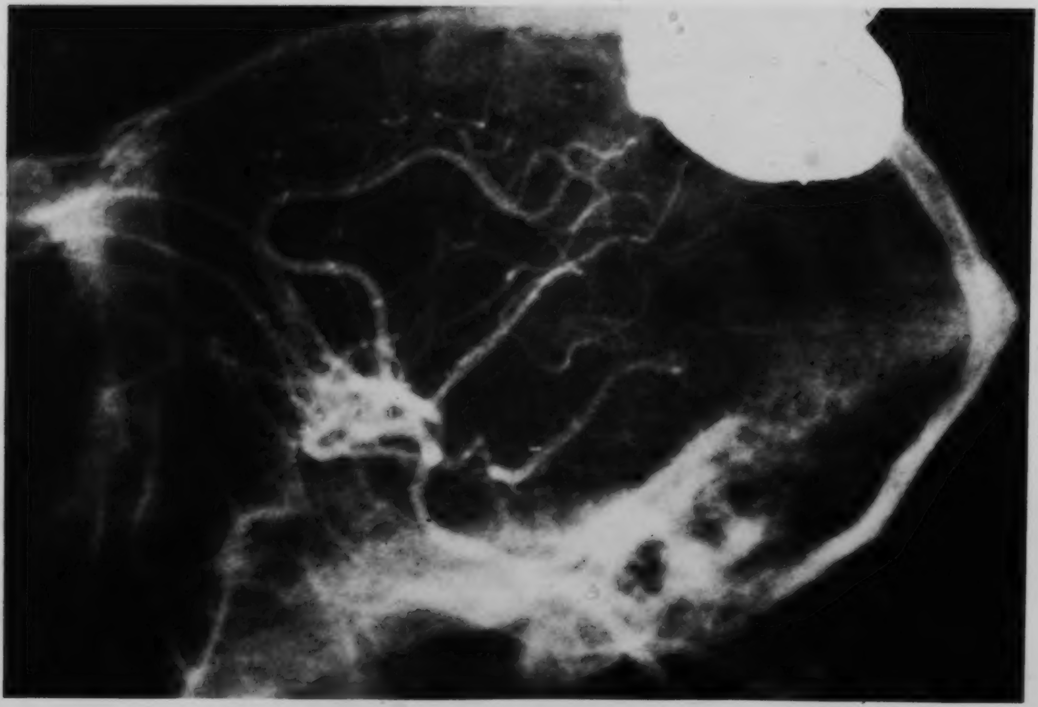


Figure 69 (a): Pre-SAH lateral cerebral angiogram for the SAH_{Rx} group.

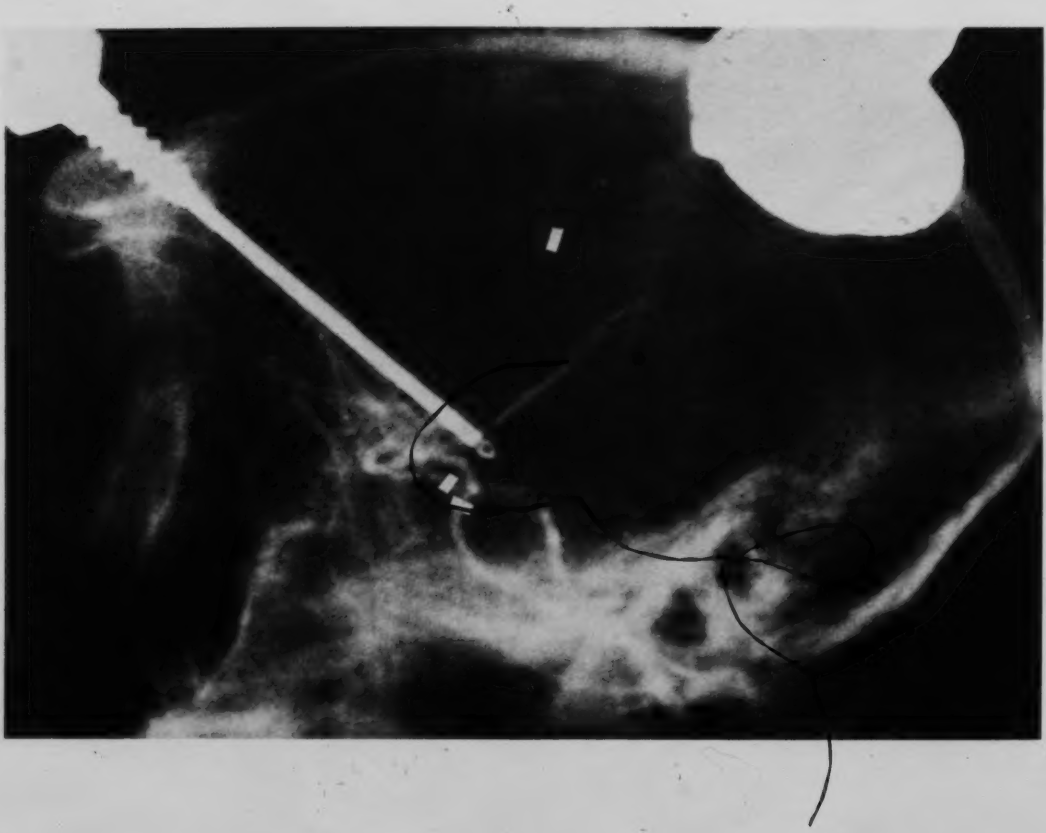


Figure 69 (b): Lateral cerebral angiogram for same animal as in Figure 69 (a) just prior to glutaraldehyde perfusion. Sites marked are areas at which the cerebral vessels were studied at E.M.

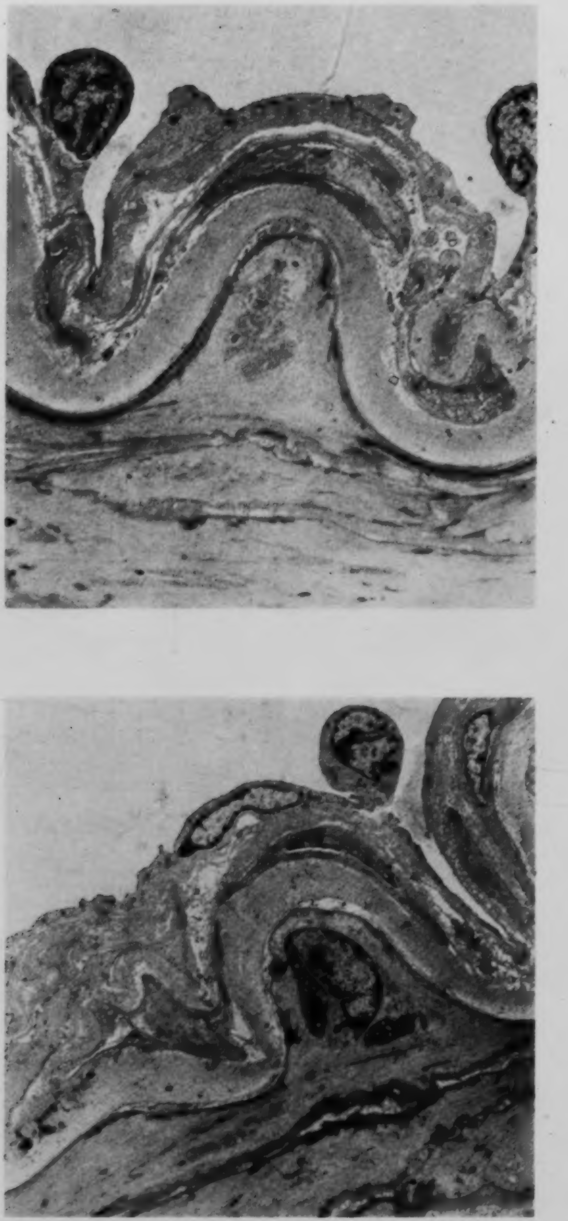
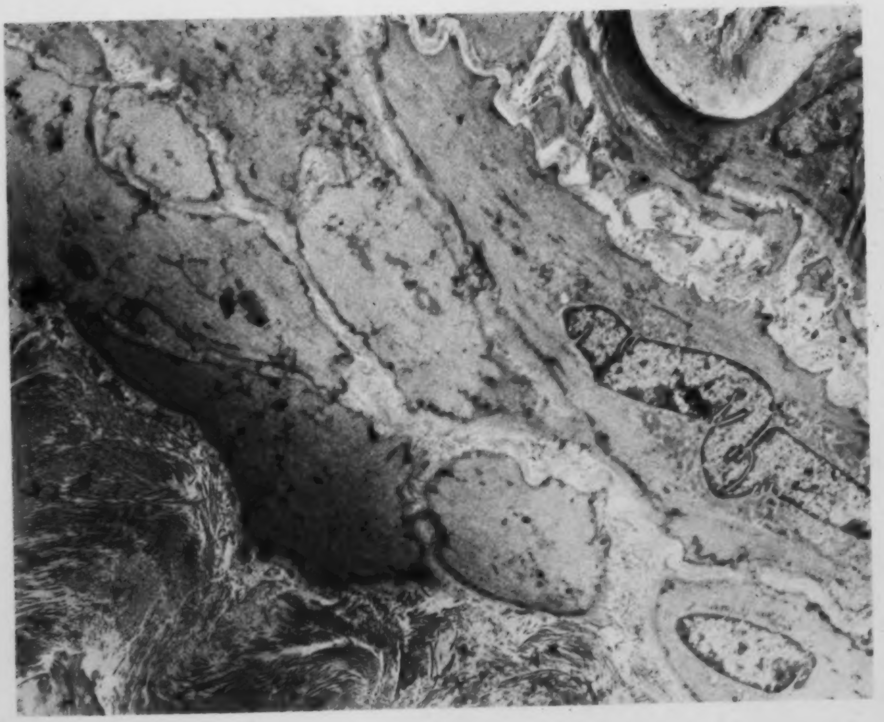


Figure 70: Arterial ultrastructure of the DPA (distal pericallosal artery) for the SAH_{Rx} group.

(a), (b): Marked intimal undulation



(c): Markedly contracted media musculature

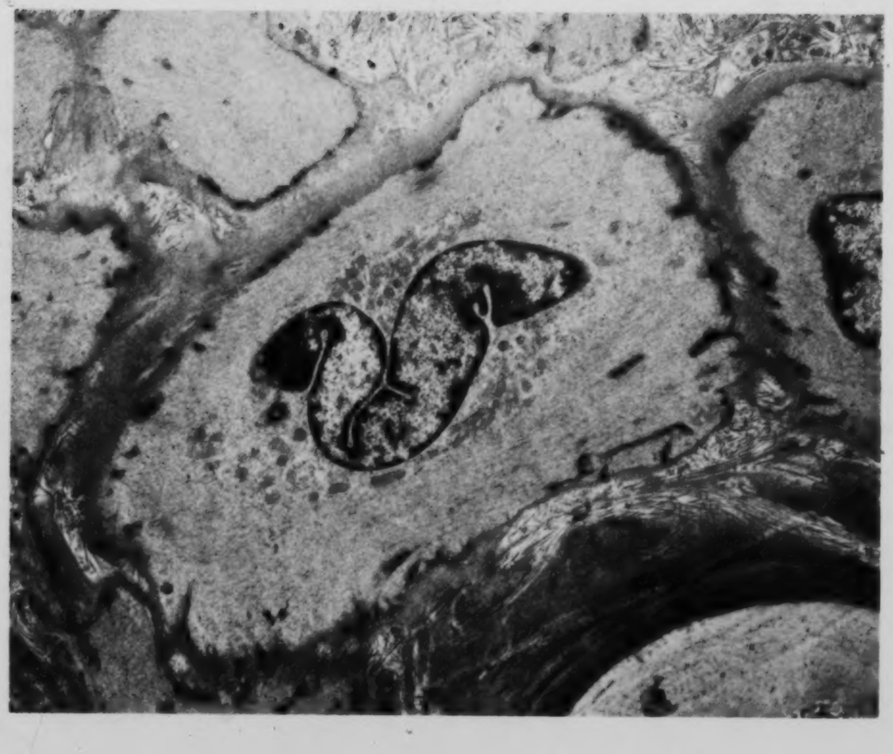


Figure 71: Markedly contracted media muscle cell with kinked nucleus from the DPA (distal pericallosal artery) of an animal in the SAH_{Rx} group.

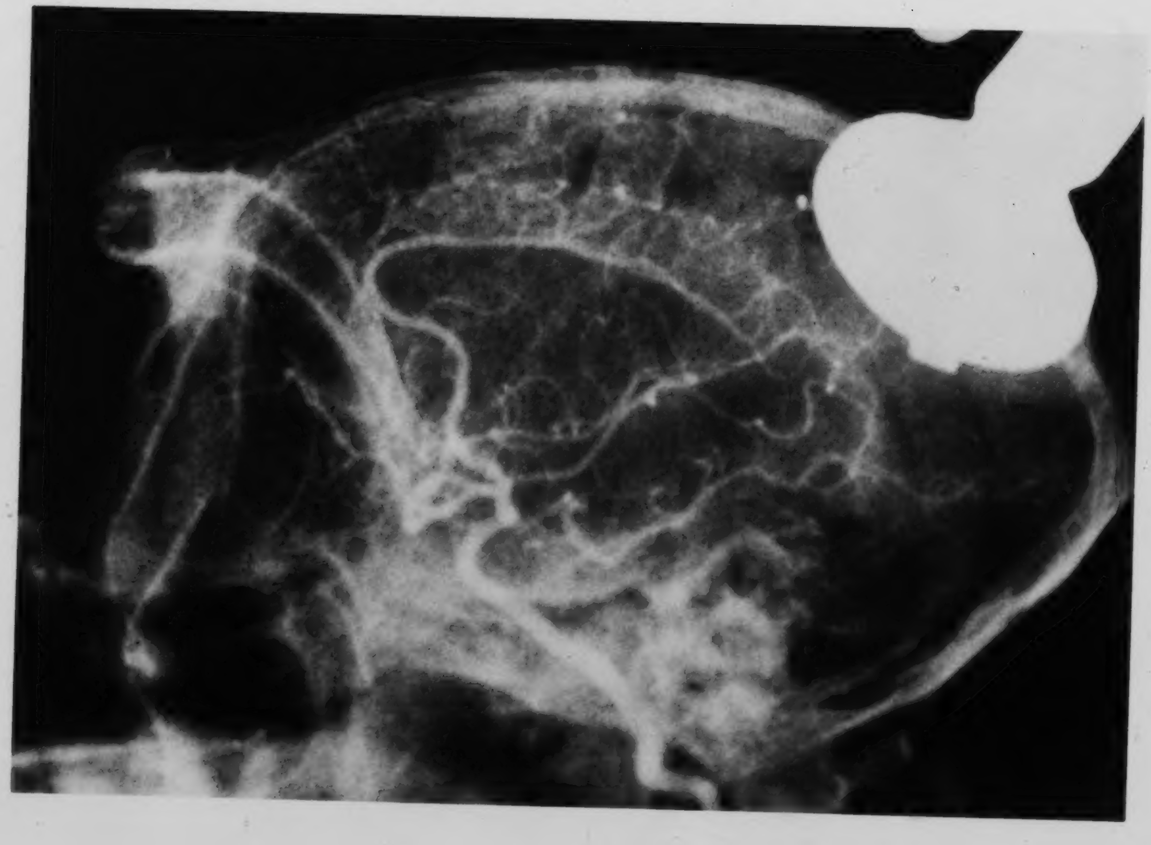


Figure 72 (a): Pre-hypothetical insult lateral cerebral angiogram of an animal in the Rx alone group.

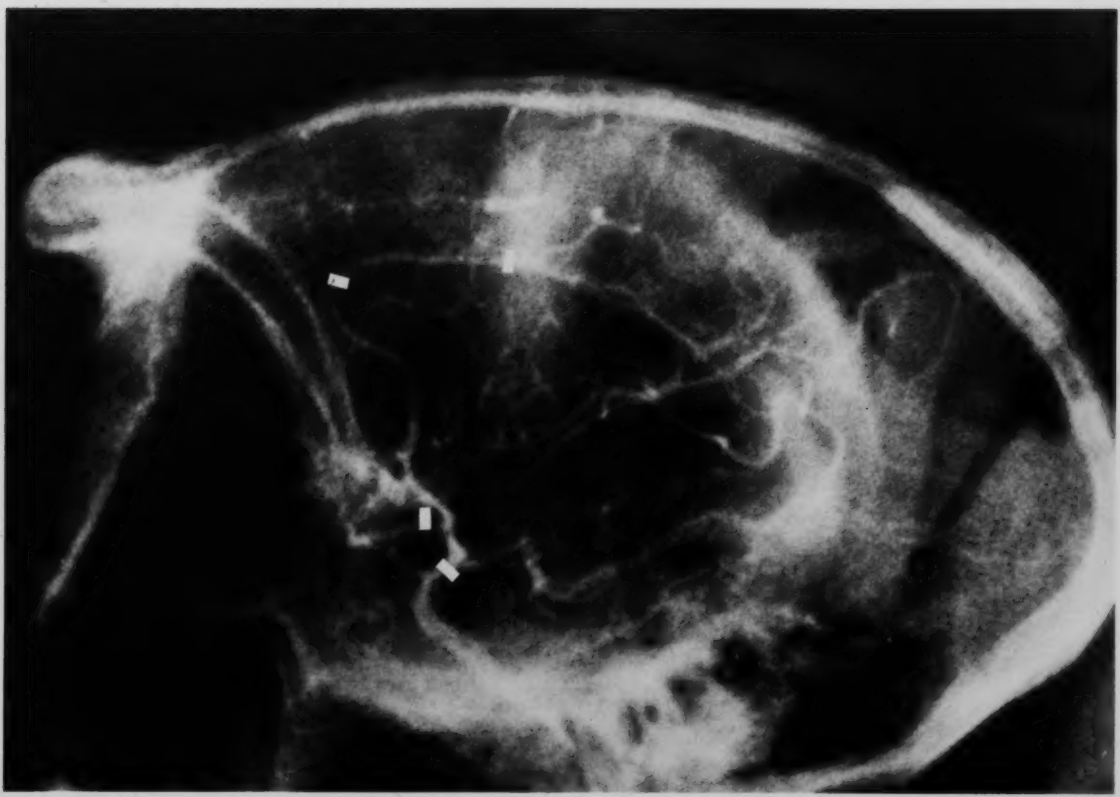


Figure 72 (b): Lateral cerebral angiogram of the same animal just prior to glutaraldehyde perfusion. Sites marked are areas at which the cerebral vessels were studied at E.M.

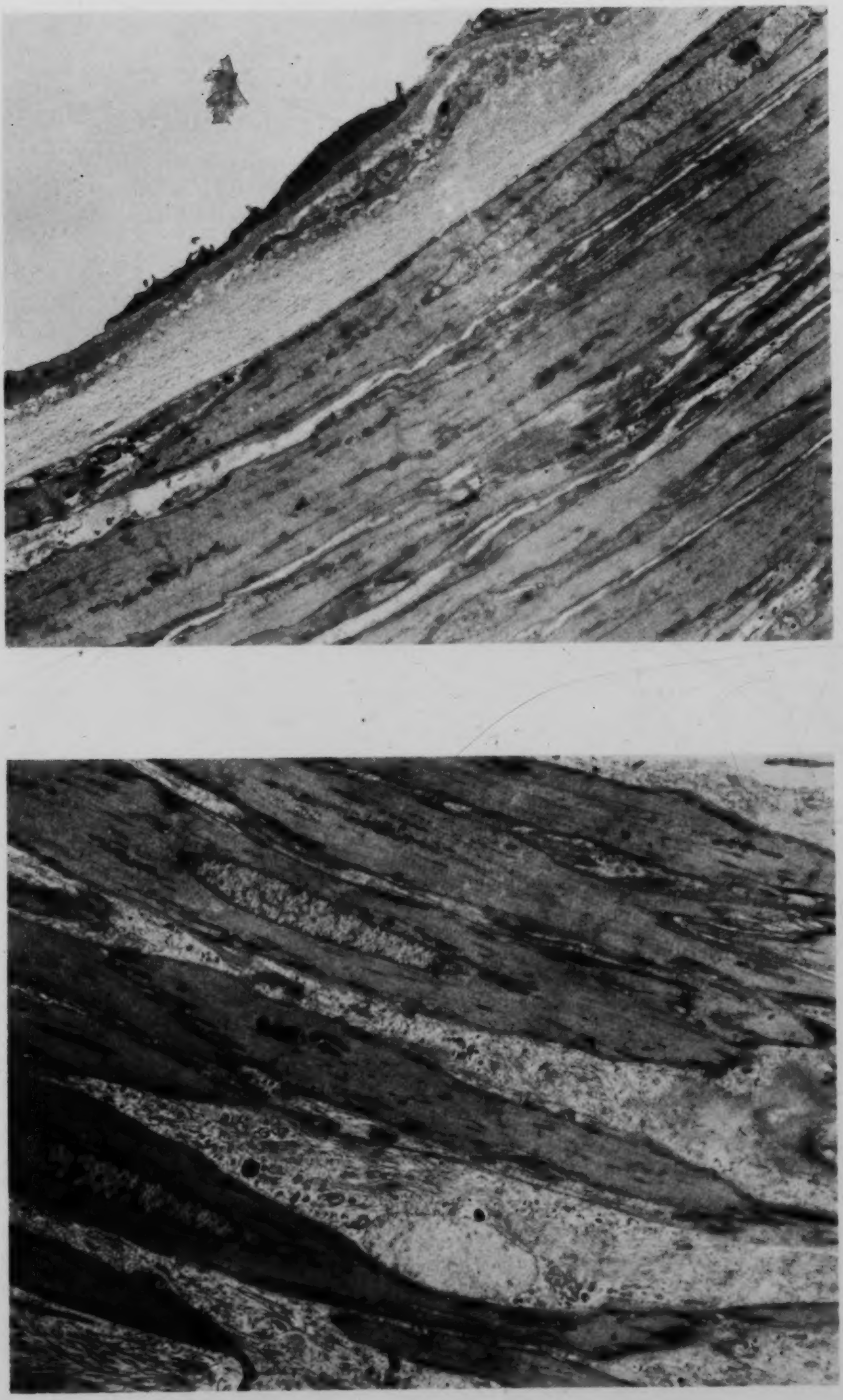


Figure 73: Arterial ultrastructure of the IDICA (intradural internal carotid artery) for the Rx alone group.

(a): Minimal intimal undulation

(b): Mild contraction of the media musculature

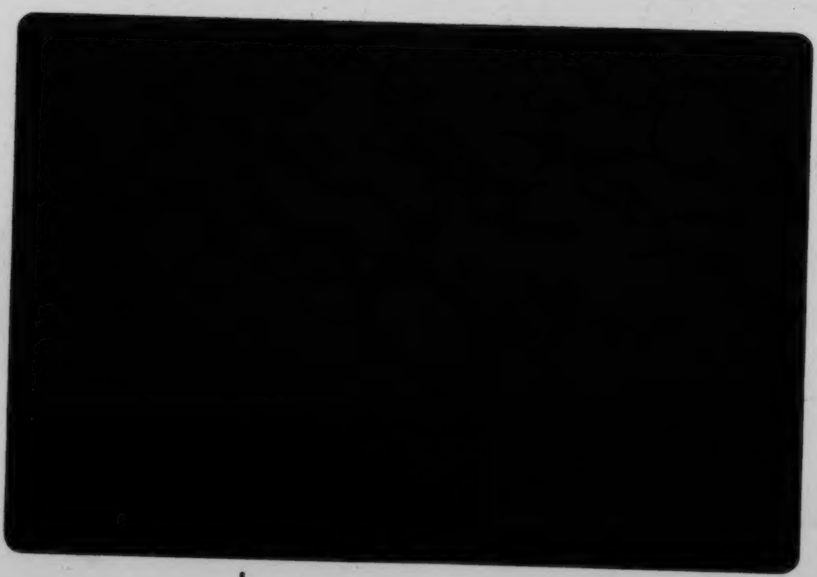


Figure 74: Histological section of pulmonary tissue from an animal in the Rx alone group demonstrating normal lung tissue.

GROUP	INSULT VOLUME (ml/kg)	n	MEAN WEIGHT (KG)
SAH	1.0	5	3.3±0.2
	1.33	5	3.0±0.1
	1.67	5	3.3±0.3
	2.0	5	3.1±0.2
SDH	1.67	2	3.0±0.3
	2.0	2	3.5±0.5
Artificial CSF	1.67	5	2.6±0.3
SAH_{Rx}	1.67	8	3.1±0.2
SDH_{Rx}	1.67	6	3.0±0.2
Rx Alone	-	3	2.7±0.5

Table 1: Mean weight and SEM of the 10 groups in this study.

GROUP	FLOW	n	MaBP mmHg	HR beats/minute	ICP mmHg	CPP mmHg	rCBF ml/100gm/min	CVR Index	VC mm
A	1	5	105±11	185±21	10±1	95±12	58±6	1.66±.18	1.18±.11
	2	5	105±10	187±22		95±10	55±5	1.73±.14	
	3	5	111±7	185±24		101±8	60±6	1.72±.13	
	4	5	103±6	175±21		93±7	56±7	1.79±.26	
	MEAN		106±4	183±10		96±4	57±3	1.73±.09	
B	1	5	87±8	193±18	13±2	75±7	64±9	1.22±.12	1.21±.05
	2	5	112±7	208±10		99±7	64±9	1.69±.28	
	3	5	104±4	211±11		90±5	59±7	1.66±.27	
	4	5	110±6	205±16		97±7	60±6	1.73±.26	
	MEAN		103±4	204±7		90±4	62±4	1.57±.12	
C	1	5	100±5	204±11	14±2	87±5	49±7	1.88±.28	1.36±.05
	2	5	99±8	210±14		85±8	51±7	1.79±.27	
	3	5	97±5	212±11		84±4	56±8	1.61±.22	
	4	5	94±5	219±13		80±4	55±7	1.57±.24	
	MEAN		98±3	211±6		84±3	53±3	1.71±.12	
D	1	5	100±13	209±12	11±2	89±14	47±4	1.96±.33	1.34±.06
	2	5	101±13	212±12		89±13	52±4	1.75±.29	
	3	5	103±11	214±10		92±12	49±3	1.91±.26	
	4	5	101±11	211±11		90±12	49±4	1.90±.27	
	MEAN		101±6	211±5		90±6	49±2	1.88±.13	
Artificial CSF	1	5	92±4	189±8	9±1	82±4	63±3	1.32±.11	1.18±.08
	2	5	94±5	198±6		85±5	63±6	1.40±.17	
	3	5	91±7	200±8		81±7	63±6	1.32±.14	
	4	5	99±7	201±9		90±7	61±5	1.50±.18	
	MEAN		94±3	197±4		85±3	63±2	1.39±.07	

A - 1.0 ml/kg; B - 1.33 ml/kg; C - 1.67 ml/kg; D -2.0 ml/kg.

Table 2: Pre-Insult MaBP, HR, ICP, CPP, rCBF, CVR, and VC of the 4 SAH volume groups and the artificial CSF group.

Group	n	Time to Change ICP	 MaBP	 R	 RVP	Time to Peak ICP	 MaPB	 RVP	Maximum Change ICP (mmHg)	 MaPB (mmHg)	 Apnea (seconds)	 RVP (mmHg)
		(-------------	seconds	------------	)	(--------	seconds	-------)				
1.0 ml/kg	5	1.6±0.4	13±3	12±3	-	19±1	49±8	-	91±10	162±13	12±6	-
1.33 ml/kg	5	2.2±0.5	9±2	10±2	-	27±4	44±6	-	134±19	174±6	26±9	-
1.67 ml/kg	5	1.2±0.2	12±3	15±1	-	33±5	64±14	-	142±17	166±8	95±6	
2.0 ml/kg	5	1.7±0.5	12±3	15±3	-	38±3	63±5	-	140±13	167±12	65±18	-
Artificial CSF	5	1.4±0.1	15±3	15±1	35±8	42±10	42±5	51±9	168±25	163±6	25±3	31±4

Table 3: "Time to change", "time to peak" and "maximum change" for ICP, MaBF, R (respiratory pattern) and RVP for the 4 SAH volume groups and the artificial CSF group subsequent to the insult.

Group	n	ICP Half-Time Decay (seconds)	Time to Recover (------ seconds ------)				MaBP - ICP (mmHg)		HR at Peak (beats /min)	
			ICP	MaBP	R	RVP	$\overline{CPP}$	$\overline{CPP_1}$	ICP	MaBP
1.0 ml/kg	5	35±18	403±157	181±54	65±10	-	48±7	96±3	160±21	185±16
1.33 ml/kg	5	44±18	536±193	190±28	111±30	-	40±5	92±4	213±12	208±18
1.67 ml/kg	5	23±12	669±140	478±142	159±12	-	28±9	92±2	252±12	201±3
2.0 ml/kg	5	18±7	553±126	282±44	124±34	-	40±9	91±9	168±48	182±20
Artificial CSF	5	8±3	95±18	327±169	62±6	142±21	32±5	98±2	202±13	190±16

Table 4: ICP half-time decay and "time to recover" to a steady state from initial change. "Time to recover" for MaBP, R (respiration) and RVP to a steady state. CPP during ICP elevation ($\overline{CPP}$) and during ICP recovery ($\overline{CPP_1}$). HR at peak ICP and MaBP.

GROUP		n	MaBP mmHg	HR beats/minute	ICP mmHg	CPP mmHg	rCBF % of pre-SAH flow	CVR Index	VC % of pre-SAH diameter
Flow 5	A	5	87±5	156±18	9±3	79±3	64±12*	2.39±.29	
	B	5	89±9*	188±15	15±4	73±7*	67±9	1.89±.08	
	C	5	74±10	196±14	13±5	60±8*	40±6*	3.88±.56	
	D	5	76±7*	183±23	14±5	62±5*	37±7+	4.35±1.26	
	ARTIFICIAL CSF	5	93±3	199±10	2±1	91±4	81±2*	1.82±.12*	
Flow 6	A	5	97±4	162±21	10±2	87±3	71±9*	2.37±.35	73±5+
	B	5	99±9	195±14	14±3	85±8	87±15	1.73±.16	76±5+
	C	5	79±11	205±18	11±3	68±11	61±11	2.68±.08	70±4+
	D	5	81±11+	207±12	14±6	67±10*	51±11+	3.41±1.13	80±7*
	ARTIFICIAL CSF	5	102±4	216±6	4±2	98±4	88±7	1.86±.22	102±4
Flow 7	A	5	103±10	157±12	7±2	95±10	79±7*	2.26±.36	
	B	5	102±9	201±13	13±3	89±10	108±20	1.45±.13	
	C	3	89±11	214±16	13±5	76±11	77±23	2.55±.41	
	D	5	98±13	175±23	12±8	86±9	64±13*	3.95±1.49	
	ARTIFICIAL CSF	5	87±5	201±5	4±2	83±4	85±8	1.61±.13	

Table 5: Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control) for CBF determinations 5, 6 and 7. (*-$p<0.05$, +-$p<0.01$).

GROUP		n	MaBP mmHg	HR beats/minute	ICP mmHg	CPP mmHg	rCBF % of pre-SAH flow	CVR Index	VC % of pre-SAH diameter
Flow 8	A	4	118±11	170±19	7±1	111±11	77±8 *	2.72±.42 +	
	B	5	102±8	205±14	13±4	89±11	108±18	1.45±.14	
	C	3	89±11	233±19	15±6	74±14	66±15	2.81±.61	
	D	3	81±14	218±21	4±2	77±16	85±4 *	1.71±.35	
ARTIFICIAL CSF		5	92±6	208±7	3±2	89±4	81±6	1.78±.07	
Flow 9	A	4	103±7	192±14	9±4	97±8	80±15	2.39±.59	
	B	5	95±5 *	204±14	13±4	81±9	101±19	1.46±.17	
	C	3	89±10	242±16	16±8	74±13	64±10	2.80±.58 *	
	D	3	77±12	225±25	5±3	72±14	80±1 +	1.69±.31	
ARTIFICIAL CSF		5	101±4	218±5 *	4±2	98±3	88±7	1.82±.12	
Flow 10	A	4	107±5	196±17	11±4	96±5	83±12	2.21±.44	90±11
	B	5	98±7 *	215±14	15±5	83±11	91±11	1.60±.24	89±6
	C	3	87±13	246±17	16±8	70±16	60±8	2.93±.84	80±4 *
	D	3	78±9	241±24	5±2	73±11	82±6	1.71±.32	85±9
ARTIFICIAL CSF		5	98±5	229±4 +	4±3	94±3	83±3	1.82±.10	97±4

Table 6: Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control) for CBF determinations 8, 9 and 10.

(*-$p<0.05$, +-$p<0.01$).

GROUP	FLOW	n	V_t (ml)	RR (breaths/minutes)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	pH	RVP (mmHg)	$A\text{-}aDO_2$ (mmHg)
A	1	5	35±2	42±14	40±2	106±6	7.39±0.02		45±8
	2	5	37±3	38±5	39±2	104±5	7.40±0.01		47±7
	3	5	35±4	40±5	39±2	109±4	7.40±0.01		43±5
	4	5	33±2	39±7	38±2	111±4	7.41±0.01		42±6
	MEAN		35±2	40±3	39±1	107±2	7.40±0.01		44±1
B	1	5	33±5	38±5	38±1	101±9	7.38±0.03		52±9
	2	5	36±5	36±3	36±2	118±14	7.38±0.03		49±5
	3	5	34±6	36±3	35±2	118±14	7.39±0.02		54±3
	4	5	37±4	32±2	36±1	125±19	7.39±0.02		50±3
	MEAN		35±2	36±2	36±1	116±7	7.38±0.01		51±1
C	1	5	33±3	37±6	36±1	111±19	7.40±0.02		51±13
	2	5	33±4	38±7	38±2	117±16	7.40±0.01		41±7
	3	5	31±3	38±6	39±1	120±17	7.40±0.01		38±10
	4	5	33±3	40±7	39±1	120±16	7.40±0.01		39±10
	MEAN		32±2	38±3	38±1	117±8	7.40±0.01		42±3
D	1	5	34±4	33±3	36±2	111±9	7.39±0.01		34±7
	2	5	35±4	33±3	36±2	122±6	7.39±0.01		32±5
	3	5	35±5	34±4	35±2	125±7	7.40±0.02		32±8
	4	5	36±5	34±3	35±2	125±7	7.40±0.02		32±7
	MEAN		35±2	33±2	35±1	121±4	7.40±0.01		33±1
Artificial CSF	1	5	25±8	35±5	47±1	110±10	7.33±0.01	22±1	42±13
	2	5	26±7	35±5	46±1	119±6	7.33±0.02	21±1	33±10
	3	5	25±8	36±5	46±1	125±6	7.33±0.02	21±1	29±7
	4	5	28±10	35±5	45±1	120±8	7.33±0.02	21±1	34±12
	MEAN		26±4	35±2	46±1	119±4	7.33±0.01	21±0	35±3

A - 1.0 ml/kg; B - 1.33 ml/kg; C - 1.67 ml/kg; D -2.0 ml/kg.

Table 7: Pre-Insult. V_t (tidal volume), RR (respiratory rate), $PaCO_2$, PaO_2, pH, RVP (right ventricular pressure) and $A\text{-}aDO_2$ (alveolar-arterial oxygen difference) for the 4 SAH volume groups and the artificial CSF group. (∗-$p<0.05$, +-$p<0.01$).

GROUP	n	V_t	RR	$PaCO_2$	PaO_2	pH	RVP (mmHg)	$A\text{-}aDO_2$ (mmHg)
		(-------------------- % of	pre - insult	--------------------	)			
Flow 5 A	5	85±5	93±8	95±3	94±8	7.38±0.01		54±7
B	5	94±7	90±7	103±9	97±5	7.36±0.02		51±2
C	5	148±24	90±16	76±9	83±13	7.44±0.05		82±4 *
D	5	142±24	98±11	91±4	90±5	7.42±0.02		50±12 *
ARTIFICIAL CSF	5	113±8	97±4	93±2	96±3	7.36±0.02	18±0 *	43±11 *
Flow 6 A	5	89±5	93±4	94±2 *	95±8	7.38±0.01		53±7
B	5	97±10	106±8	106±13	100±6	7.33±0.01		44±5
C	3	91±10	93±16	84±6	68±13	7.41±0.02		85±14
D	5	103±8	97±5	89±6	83±10	7.39±0.02		58±19
ARTIFICIAL CSF	5	119±7	104±6	93±2	100±4	7.35±0.02	20±1	38±11
Flow 7 A	5	96±5	90±10	102±3	98±10	7.37±0.01		46±12
B	5	90±11	98±3	114±14	100±6	7.33±0.03		40±4 *
C	3	95±8	91±17	95±7	89±19	7.37±0.03		69±26
D	5	81±10	95±6	97±4	82±11	7.33±0.04		56±19
ARTIFICIAL CSF	5	99±16	98±6	95±3	97±3	7.34±0.01	20±1	40±8

Table 8: Post-Insult. V_t, RR, $PaCO_2$ and PaO_2 as % of control, and pH, RVP and $A\text{-}aDO_2$ for CBF determinations 5, 6 and 7. (*-$p<0.05$, +-$p<0.01$).

GROUP		n	V_t	RR	$PaCO_2$	PaO_2	pH	RVP (mmHg)	$A\text{-}aDO_2$ (mmHg)
			(---------------------% of pre - insult			------------------)			
Flow 8	A	4	98±11	89±6	98±4	104±8	7.40±0.01		42±10
	B	5	90±9	98±4	112±14	97±6	7.34±0.02		43±3 *
	C	3	113±9	90±14	95±6	88±16	7.38±0.02		66±20
	D	3	92±10	106±14	94±2	98±3	7.37±0.03		29±3
ARTIFICIAL CSF		5	90±12	106±6	93±3	98±4	7.35±0.01	20±1	40±8
Flow 9	A	4	93±5	109±12	90±5	101±8	7.43±0.01		48±11
	B	5	95±11	95±6	106±11	103±5	7.35±0.01		40±5 *
	C	3	116±6	90±15	92±7	93±11	7.38±0.01		57±10
	D	3	87±11	104±13	94±2	95±3	7.35±0.04		33±6
ARTIFICIAL CSF		5	102±11	113±4	88±1 +	95±3	7.36±0.02 *	21±1	46±10
Flow 10	A	4	97±4	109±6	91±8	102±9	7.42±0.01		46±12
	B	5	102±10	101±4	102±6	102±8	7.35±0.01		42±6
	C	3	117±7	94±14	90±5	97±4	7.38±0.03		53±1
	D	3	101±10	102±11	90±4	100±1	7.36±0.02		28±2
ARTIFICIAL CSF		5	109±13	119±8	88±2 *	92±3	7.35±0.01	21±1	49±11 +

Table 9: Post-Insult. V_t, RR, $PaCO_2$ and PaO_2 as % of control, and pH, RVP and $A\text{-}aDO_2$ for CBF determinations 8, 9 and 10. (* -$p<0.05$, + -$p<0.01$).

GROUP	FLOW	n	MaBP (mmHg)	HR beats/minute	ICP (mmHg)	CPP (mmHg)	rCBF ml/100 gm/min	CVR Index	VC (mm)
SDH(ml/kg)									
	1	2	98±23	162±48		87±24	41±1	2.15±.61	
	2	2	113±17	201±33		102±18	46±7	2.33±.75	
1.67	3	2	106±18	207±33		95±19	47±11	2.25±.92	
	4	2	110±12	195±27	11±1	99±13	43±7	2.42±.70	1.32±.11
	MEAN		107±7	191±15		96±7	44±3	2.26±.33	
	1	2	107±7	207±3		95±7	66±11	1.46±.14	
2.0	2	2	98±8	219±3		86±8	76±12	1.15±.08	
	3	2	107±10	213±3		93±8	77±7	1.22±.21	
	4	2	98±2	213±3	12±0	86±2	74±7	1.18±.13	1.33±.10
	MEAN		102±3	213±2		90±3	73±4	1.25±.07	

Table 10: Pre-Insult. MaBP, HR, ICP, CPP, rCBF, CVR and VC (vessel caliber) for the 1.67 and 2.0 ml/kg SDH groups.

Group	n	Time to Change			Time to Peak		Maximum Change		
		ICP	MaBP (seconds)	R	ICP	MaBP (seconds)	ICP (mmHg)	MaBP (mmHg)	Apnea (seconds)
SDH (ml/kg)									
1.67	2	1.5±0.5	9±1	20±6	37±15	71±22	123±3	155±23	43±12
2.0	2	2.0±1.0	7±1	9±4	39±4	46±6	120±0	173±1	37±9

Table 11: "Time to change", "time to peak" and "maximum change" for ICP, MaBP and R (respiratory pattern) of the 1.67 and 2.0 ml/kg SDH groups.

Group	n	ICP Half-Time Decay (seconds)	Time to Recover (seconds)			MaBP - ICP (mmHg)		HR at Peak (beats/min)	
SDH (ml/kg)			ICP	MaBP	R	$\overline{CPP}$	$\overline{CPP}_1$	ICP	MaBP
1.67	2	9±5	248±52	282±44	77±9	44±5	86±15	98±2	104±14
2.0	2	19±7	115±15	235±17	60±9	43±10	90±12	-	-

Table 12: ICP half-time decay and "time to recover" to a steady state from initial change. "Time to recover" for MaBP and R to a steady state. CPP during ICP elevation $\overline{CPP}$ and recovery $\overline{CPP}_1$. HR at peak ICP and MaBP.

GROUP	FLOW	n	MaBP (mmHg)	HR beats/minute	ICP (mmHg)	CPP (mmHg)	rCBF % of pre-SDH flow	CVR Index	VC % of pre-SDH diameter
SDH(ml/kg)									
1.67	5	2	80±3	153±3	7±1	73±2	92±3	1.85±.34	
2.0	5	2	89±1	216±0	9±3	77±6	43±16	2.80±.93	
1.67	6	2	96±6	183±9	8±0	88±6	96±4	2.17±.53	83±7
2.0	6	2	90±0	213±3	7±1	83±1	53±14	2.28±.28	73±18
1.67	7	2	93±17	198±12	9±3	84±14	104±8	1.90±.44	
2.0	7	2	89±2	222±0	7±1	82±1	60±6	1.90±.04	
1.67	8	2	102±10	201±33	12±6	90±4	103±14	2.12±.64	
2.0	8	2	88±3	225±3	10±4	78±2	57±9	1.92±.04	
1.67	9	2	102±12	207±33	12±6	90±6	100±8	2.15±.59	
2.0	9	2	86±6	228±12	10±4	76±2	63±14	1.73±.22	
1.67	10	2	102±12	213±33	13±7	89±5	95±8	2.24±.59	96±9
2.0	10	1	86	240	18	60	41	2.00	76±5

Table 13: Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control).

GROUP	FLOW	n	V_t (ml)	RR (breaths/minute)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	pH	$A\text{-}aDO_2$ (mmHg)
SDH (ml/kg) 1.67	1	2	37±4	25±1	40±3	126±6	7.40±0.04	25±9
	2	2	40±4	25±1	39±2	130±10	7.40±0.04	22±12
	3	2	41±6	25±1	39±2	132±8	7.38±0.00	20±10
	4	2	37±6	26±1	40±3	128±4	7.38±0.00	22±8
	MEAN		39±2	25±0	39±1	129±3	7.39±0.01	22±4
2.0	1	2	31±3	44±8	39±3	122±17	7.34±0.04	30±14
	2	2	35±2	41±3	38±3	116±11	7.34±0.04	37±8
	3	2	34±1	50±10	40±2	112±7	7.34±0.04	39±5
	4	2	29±2	49±11	39±3	110±5	7.34±0.04	42±3
	MEAN		32±1	46±4	39±1	115±5	7.34±0.02	37±4

Table 14: Pre-Insult. V_t (tidal volume), RR (respiratory rate), $PaCO_2$, PaO_2, pH and $A\text{-}aDO_2$ (alveolar-arterial oxygen difference) for the 1.67 and 2.0 ml/kg SDH groups.

GROUP	FLOW	n	V_t	RR	$PaCO_2$	PaO_2	pH	$A\text{-}aDO_2$ (mmHg)
			(------------------------	% of pre- SDH value	-----------------	)		
SDH ml/kg								
1.67	5	2	88±10	97±7	77±4	98±5	7.41±0.05	34±7
2.0	5	2	99±4	96±1	86±2	95±8	7.38±0.02	51±4
1.67	6	2	88±9	95±5	84±5	93±6	7.38±0.03	40±1
2.0	6	2	87±14	89±5	106±17	90±4	7.34±0.04	46±6
1.67	7	2	88±3	99±1	92±8	96±6	7.39±0.06	31±5
2.0	7	2	85±1	84±5	96±7	89±1	7.34±0.02	52±2
1.67	8	2	85±4	108±8	95±8	94±2	7.39±0.06	32±11
2.0	8	2	96±1	97±3	92±11	98±5	7.39±0.02	42±5
1.67	9	2	90±5	112±4	89±11	96±3	7.40±0.06	33±11
2.0	9	2	87±0	96±15	97±5	100±2	7.41±0.01	38±7
1.67	10	2	90±1	104±4	93±7	98±4	7.41±0.05	28±8
2.0	10	1	84	116	102	97	7.38	46

Table 15: Post-Insult. V_t, RR, $PaCO_2$ and PaO_2 as % of control, and pH and $A\text{-}aDO_2$ for CBF determinations 5 - 10.

GROUP	n	MEAN GRADE 5 HOURS	MEAN GRADE 20 HOURS
SAH			
1.0 ml/kg	5	1.8	2.6
1.33 ml/kg	5	2.2	2.6
1.67 ml/kg	5	4.0	5.0
2.0 ml/kg	5	4.5	5.0
SDH			
1.67 ml/kg	2	1.5	1.0
2.0 ml/kg	2	1.0	3.0
ARTIFICIAL CSF	5	1.6	1.0 *

* 4 animals.

Table 16: Neurological grade at 5 hours and 20 hours post-insult for the 4 SAH volume, SDH volume and artificial CSF groups.

GROUP	FRESH WET BRAIN WEIGHT	$\frac{\text{BRAIN WEIGHT(gm)}}{\text{BODY WEIGHT(kg)}}$	FORMALDEHYDE BRAIN WEIGHT GAIN (gm)
SAH			
1.0 ml/kg	62.1±4.9 (2)	19.7±0 (2)	6.5 (1)
1.33 ml/kg	59.6±8.0 (2)	19.8±2.0 (2)	4.4 (2)
1.67 ml/kg	61.7±2.3 (2)	19.9±0.1 (2)	2.2 (1)
2.0 ml/kg	58.4±2.5 (4)	19.0±1.0 (4)	7.2 (4)
Artificial CSF	60.6 (1)	27.5 (1)	3.5 (1)

Table 17: Mean fresh wet brain weight, brain weight/body weight, and formaldehyde brain weight gain for the 4 SAH volume groups and the artificial CSF group.

GROUP	IDICA	MCA	PPA	DPA
SAH (ml/kg)				
1.0	1	1	1	1
1.33	1	1	0	0
1.67	3	2	3	1
2.0	-	-	-	-
SDH (ml/kg)				
1.67	1	0	0	-
2.0	-	-	-	-
ARTIFICIAL CSF	1	1	0	1
SAH_{Rx}	-	2	3	3
SDH_{Rx}	-	-	-	-
Rx alone	1	1	1	1

Table 18: Degree of vasoconstriction of cerebral vessels studied at E. M. for all groups in this study. (IDICA - intradural internal carotid artery, MCA - middle cerebral artery, PPA - proximal pericallosal artery and DPA - distal pericallosal artery).

GROUP	FLOW	n	MaBP (mmHg)	HR beats/minute	ICP (mmHg)	CPP (mmHg)	rCBF (ml/100g/min)	CVR Index	VC (mm)
SAH_{R_X}	1	8	98±7	198±7		84±7	58±4	1.53±0.20	
	2	8	93±6	199±7		80±6	54±5	1.53±0.16	
	3	8	100±7	202±6		87±7	56±4	1.62±0.20	
	4	8	102±8	201±7	13±1	87±8	53±5	1.71±0.20	1.16±0.06
	MEAN		98±3	199±3		85±3	55±2	1.60±0.09	
SAH	1	5	100±5	204±11		87±5	49±7	1.88±0.28	
	2	5	99±8	210±14		85±8	51±7	1.79±0.27	
	3	5	97±5	212±11		84±4	56±8	1.61±0.22	
	4	5	94±5	219±13	14±2	80±4	55±7	1.57±0.24	1.36±0.05
	MEAN		98±3	211±6		84±3	53±3	1.71±0.12	
ARTIFICIAL CSF	1	5	92±4	189±8		82±4	63±3	1.32±0.11	
	2	5	94±5	198±6		85±5	63±6	1.40±0.17	
	3	5	91±7	200±8		81±7	63±6	1.32±0.14	
	4	5	99±7	201±9	9±1	90±7	61±5	1.50±0.18	1.18±0.08
	MEAN		94±3	197±4		85±3	63±2	1.39±0.07	

Table 19: Pre-Insult. MaBP, HR, ICP, CPP, rCBF, CVR and VC (vessel caliber) for the SAH_{R_X}, 1.67 ml/kg SAH and artificial CSF groups.

Group	n	Time to Change ICP (--------	 MaBP seconds	 R --------	 RVP --------)	Time to Peak ICP (-------	 MaBP seconds	 RVP -------)	Maximum Change ICP (mmHg)	 MaBP (mmHg)	 Apnea (seconds)	 RVP (mmHg)
SAH_{Rx}	8	1.4±0.1	11±2	10±1	31±9	50±6	66±10	81±12	193±11	177±9	56±10	34±4
SAH	5	1.2±0.2	12±3	15±1	-	33±5	64±14	-	142±17	166±8	95±6	-
Artificial CSF	5	1.4±0.1	15±3	15±1	35±8	42±10	42±5	57±9	168±25	163±6	25±3	31±4
SDH_{Rx}	6	1.3±0.2	14±3	11±2	28±5	43±8	53±10	68±13	178±17	180±5	39±12	38±5

Table 20: "Time to change", "time to peak" and "maximum change" for ICP, MaBP, R (respiratory pattern) and RVP for the SAH_{R_X}, 1.67 ml/kg SAH, SDH_{R_X} and artificial CSF groups subsequent to the insult.

Group	n	ICP Half-time Decay (seconds)	Time to Recover				CPP	$\overline{CPP_1}$	HR at Peak	
			ICP (---	MaBP	R	RVP ---)	MaBP - ICP (mmHg)		ICP (beats/min)	MaBP
			seconds							
SAH_{Rx}	8	27±10	644±167	317±50	116±12	272±68	20±5	79±7	152±26	155±22
SAH	5	23±12	669±140	478±142	159±12	-	28±9	92±2	252±12	201±3
Artifical CSF	5	8±3	95±18	327±169	62±6	142±21	32±5	98±2	202±13	190±16
SDH_{Rx}	6	19±2	312±141	229±42	107±18	206±69	24±5	76±5	200±13	200±6

Table 21: ICP half-time decay and "time to recover" to a steady state from initial change. "Time to recover" for MaBP, R (respiratory pattern) and RVP to a steady state. CPP during ICP elevation $\overline{CPP}$ and recovery $\overline{CPP_1}$. HR at peak ICP and MaBP.

GROUP	FLOW	n	MaBP (mmHg)	HR beats/minute	ICP (mmHg)	CPP (mmHg)	rCBF % of pre-insult flow	CVR Index	VC % of pre-insult diameter
SAH_{RX}	5	8	74±9^{+}	188±7	12±4	63±8^{+}	44±6^{+}	2.98±0.19^{+}	
SAH	5	5	74±10	196±14	13±5	60±8*	40±6*	3.88±0.56	
Artificial CSF	5	5	93±3	199±10	2±1	91±4	81±2*	1.82±0.12*	
SAH	6	3	79±11	205±18	11±3	68±11	61±11	2.68±0.08	70±4^{+}
Artificial CSF	6	5	102±4	216±6	4±2	98±4	88±7	1.86±0.22	102±4
SAH_{RX}	6	8	75±6^{+}	212±8	11±4	62±7^{+}	56±4^{+}	2.34±0.32	68±4^{+}
SAH	7	3	89±11	214±16	13±5	76±11	77±23	2.55±0.41	
Artificial CSF	7	5	87±5	201±5	4±2	83±4	85±8	1.61±0.13	
SAH_{RX}	7	8	76±6^{+}	201±10	10±2	65±7^{+}	58±6^{+}	2.23±0.35	
SAH	8	3	89±11	233±19	15±6	74±14	66±15	2.81±0.61	
Artificial CSF	8	5	92±6	208±7	3±2	89±4	81±6	1.78±0.07	
SAH_{RX}	8	7	78±8^{+}	216±12	17±4	61±7^{+}	55±7^{+}	2.10±0.20	
SAH	9	3	89±10	242±16	16±8	74±13	64±10	2.80±0.58*	
Artificial CSF	9	5	101±4	218±5*	4±2	98±3	88±7	1.82±0.12	
SAH_{RX}	9	7	74±8^{+}	207±20	11±3	62±6^{+}	51±6^{+}	2.34±0.24	
SAH	10	3	87±13	246±17	16±8	70±16	60±8	2.93±0.84	80±4*
Artificial CSF	10	5	98±5	229±4^{+}	4±3	94±3	83±3	1.82±0.10	97±4
SAH_{RX}	10	6	77±6^{+}	224±11	9±1	69±7*	50±6^{+}	2.53±0.30*	80±7*
SAH_{RX}	11	6	94±9	220±14	5±3	91±12	58±6^{+}	3.19±0.36^{+}	86±7

Table 22: Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control) at CBF determinations 5 - 10 for the 1.67 ml/kg SAH and artificial CSF groups and 5 - 11 for the SAH_{RX}. ($*$-$p<0.05$, $+$-$p<0.01$).

GROUP	FLOW	n	V_t (ml)	RR breaths/minute	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	pH	RVP (mmHg)	$A\text{-}aDO_2$ (mmHg)
SAH_{RX}	1	8	19±1	35±2	42±2	113±2	7.34±0.02	22±1	36±3
	2	8	20±2	37±2	43±1	116±3	7.33±0.03	23±1	32±4
	3	8	22±2	38±2	41±1	114±3	7.35±0.02	22±1	39±4
	4	8	21±1	38±2	40±1	115±3	7.35±0.01	18±1	37±4
	MEAN		20±1	37±1	42±1	115±1	7.34±0.01	21±1	36±2
SAH	1	5	33±3	37±6	36±1	111±19	7.40±0.02		51±13
	2	5	33±4	38±7	38±2	117±16	7.40±0.01		41±7
	3	5	31±3	38±6	39±1	120±17	7.40±0.01		38±10
	4	5	33±3	40±7	39±1	120±16	7.40±0.01		39±10
	MEAN		32±2	38±3	38±1	117±8	7.40±0.01		42±3
ARTIFICIAL CSF	1	5	25±8	35±5	47±1	110±10	7.33±0.01	22±1	42±13
	2	5	26±7	35±5	46±1	119±6	7.33±0.02	21±1	33±10
	3	5	25±8	36±5	46±1	125±6	7.33±0.02	21±1	29±7
	4	5	28±10	35±5	45±1	120±8	7.33±0.02	21±1	34±12
	MEAN		26±4	35±2	46±1	119±4	7.33±0.01	21±0	35±3

Table 23: Pre-Insult. V_t (tidal volume), RR (respiratory rate), $PaCO_2$, PaO_2, pH, RVP (right ventricular pressure) and $A\text{-}aDO_2$ (alveolar-arterial oxygen difference) for the SAH_{RX}, 1.67 ml/kg SAH and artificial CSF groups.

GROUP	FLOW	n	V_t	RR	$PaCO_2$	PaO_2	pH	RVP (mmHg)	A-aDO$_2$ (mmHg)
			(--------------- % of pre-SAH Value			--------------------)			
SAH$_{RX}$	5	8	119±9	90±9	85±4 *	97±3	7.37±0.01	17±2	46±7
SAH	5	5	148±24	90±16	76±9	83±13	7.44±0.05		82±4 *
Artificial CSF	5	5	113±8	97±4	93±2	96±3	7.36±0.02	18±0 *	43±11 *
SAH	6	3	91±10	93±16	84±6	68±13	7.41±0.02		85±14
Artificial CSF	6	5	119±7	104±6	93±2	104±4	7.35±0.02	20±1	38±11
SAH$_{RX}$	6	8	109±10	100±7	91±3	92±4	7.36±0.01	16±1 *	48±9
SAH	7	3	95±8	91±17	95±7	89±19	7.37±0.03		69±26
Artificial CSF	7	5	99±16	98±6	95±3	97±3	7.34±0.01	20±1	40±8
SAH$_{RX}$	7	8	95±7	102±7	91±2	93±5	7.35±0.01	15±1 *	55±10
SAH	8	3	113±9	90±14	95±6	88±16	7.38±0.02		66±20
Artificial CSF	8	5	90±12	106±6	93±3	98±4	7.35±0.01	20±1	40±8
SAH$_{RX}$	8	7	100±10	102±10	85±2 +	94±6	7.38±0.01	17±2	49±9
SAH	9	3	116±6	90±15	92±7	93±11	7.38±0.01		57±10
Artificial CSF	9	5	102±11	113±4	88±1 +	95±3	7.36±0.02 *	21±1	46±10
SAH$_{RX}$	9	7	114±16	98±13	78±4 *	92±7	7.41±0.02	16±2	55±10 *
SAH	10	3	117±7	94±14	90±5	97±4	7.38±0.03		53±1
Artificial CSF	10	5	109±13	119±8	88±2 *	92±3	7.35±0.01	21±1	49±1 +
SAH$_{RX}$	10	6	103±8	106±10	75±3 +	94±6	7.38±0.02	17±2	56±9
SAH$_{RX}$	11	6	108±15	114±12	79±3 *	97±5	7.38±0.02	21±2	52±8

Table 24: Post-Insult. V_t, RR, $PaCO_2$ and PaO_2 as % of control, and pH, RVP and A-aDO$_2$ for CBF determinations 5 - 10 for the 1.67 ml/kg SAH and artificial CSF groups, and 5 - 11 for the SAH$_{RX}$ group. (* - $p<0.05$, + - $p<0.01$).

GROUP	FLOW	n	MaBP (mmHg)	HR beats/minute	ICP (mmHg)	CPP (mmHg)	rCBF (ml/100g/min)	CVR Index	VC (mm)
SDH_{R_X}	1	6	103±5	178±16		92±5	58±3	1.63±0.15	
	2	6	102±4	187±9		90±4	60±6	1.61±0.23	
	3	6	97±4	178±20		85±5	60±5	1.51±0.22	
	4	6	104±6	182±17	12±1	92±6	52±4	1.84±0.21	1.27±0.02
	MEAN		101±2	181±7		90±2	58±2	1.65±0.10	
SAH_{R_X}	1	8	98±7	198±7		84±7	58±4	1.53±0.20	
	2	8	93±6	199±7		80±6	54±5	1.53±0.16	
	3	8	100±7	202±6		87±7	56±4	1.62±0.20	
	4	8	102±8	201±7	13±1	87±8	53±5	1.71±0.20	1.16±0.06
	MEAN		98±3	199±3		85±3	55±2	1.60±0.09	

Table 25: Pre-Insult. MaBP, HR, ICP, CPP, rCBF, CVR and VC (vessel caliber) for the SDH_{R_X} and SAH_{R_X} groups.

GROUP	FLOW	n	MaBP mmHg	HR beats/minute	ICP mmHg	CPP mmHg	rCBF % of pre-insult Flow	CVR Index	VC % of pre-insult diameter
SDH$_{Rx}$	5	6	$81 \pm 4^{*}$	$151 \pm 20^{*}$	9 ± 5	72 ± 3	$44 \pm 7^{+}$	$3.11 \pm 0.30^{+}$	
SAH$_{Rx}$	5	8	$74 \pm 9^{+}$	188 ± 7	12 ± 4	$63 \pm 8^{+}$	$44 \pm 6^{+}$	$2.98 \pm 0.19^{+}$	
SDH$_{Rx}$	6	6	$85 \pm 3^{+}$	193 ± 15	13 ± 3	$72 \pm 5^{*}$	$62 \pm 4^{+}$	2.04 ± 0.10	$76 \pm 5^{+}$
SAH$_{Rx}$	6	8	$75 \pm 6^{+}$	212 ± 8	11 ± 4	$62 \pm 7^{+}$	$56 \pm 4^{+}$	2.34 ± 0.32	$68 \pm 4^{+}$
SDH$_{Rx}$	7	6	$84 \pm 4^{*}$	183 ± 15	14 ± 4	70 ± 6	$71 \pm 3^{+}$	1.73 ± 0.12	
SAH$_{Rx}$	7	8	$76 \pm 6^{+}$	201 ± 10	10 ± 2	$65 \pm 7^{+}$	$58 \pm 6^{+}$	2.23 ± 0.35	
SDH$_{Rx}$	8	6	$82 \pm 4^{*}$	197 ± 14	19 ± 5	63 ± 6	$67 \pm 6^{+}$	1.69 ± 0.18	
SAH$_{Rx}$	8	7	$78 \pm 8^{+}$	216 ± 12	17 ± 4	$61 \pm 7^{+}$	$55 \pm 7^{+}$	2.10 ± 0.20	
SDH$_{Rx}$	9	6	$84 \pm 4^{*}$	205 ± 14	23 ± 3	$61 \pm 5^{+}$	$65 \pm 4^{+}$	1.67 ± 0.13	
SAH$_{Rx}$	9	7	$74 \pm 8^{+}$	207 ± 20	11 ± 3	$62 \pm 6^{+}$	$51 \pm 6^{+}$	2.34 ± 0.24	
SDH$_{Rx}$	10	6	$83 \pm 3^{*}$	209 ± 15	21 ± 6	$62 \pm 6^{*}$	$69 \pm 3^{+}$	1.59 ± 0.16	90 ± 4
SAH$_{Rx}$	10	6	$77 \pm 6^{+}$	224 ± 11	9 ± 1	$69 \pm 7^{*}$	$50 \pm 6^{+}$	$2.53 \pm 0.30^{*}$	$80 \pm 7^{*}$
SDH$_{Rx}$	11	6	93 ± 5	211 ± 16	19 ± 5	74 ± 4	$67 \pm 4^{+}$	2.03 ± 0.25	92 ± 4
SAH$_{Rx}$	11	6	94 ± 9	220 ± 14	5 ± 3	91 ± 12	$58 \pm 6^{+}$	$3.19 \pm 0.36^{+}$	86 ± 7

Table 26: Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control) for CBF determinations 5 - 11.

(*-$p<0.05$, +-$p<0.01$).

GROUP	FLOW	n	V_t (ml)	RR breaths/minute	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	pH	RVP (mmHg)	A-aDO_2 (mmHg)
SDH_{R_X}	1	6	20±2	31±2	40±1	114±3	7.34±0.01	23±1	39±2
	2	6	22±3	31±2	40±1	115±3	7.35±0.01	23±1	39±3
	3	6	21±2	32±3	40±1	112±4	7.34±0.01	23±1	40±4
	4	6	20±2	31±3	40±1	114±3	7.35±0.01	23±2	39±3
	MEAN		21±1	31±1	40±0	113±2	7.34±0.00	23±1	39±0
SAH_{R_X}	1	8	19±1	35±2	42±2	113±2	7.34±0.02	22±1	36±3
	2	8	20±2	37±2	43±1	116±3	7.33±0.03	23±1	32±4
	3	8	22±2	38±2	41±1	114±3	7.35±0.02	22±1	39±4
	4	8	21±1	38±2	40±1	115±3	7.35±0.01	18±1	37±4
	MEAN		20±1	37±1	42±1	115±1	7.34±0.01	21±1	36±2

Table 27: Pre-Insult. V_t (tidal volume), RR (respiratory rate), $PaCO_2$, PaO_2, pH, RVP (right ventricular pressure) and A-aDO_2 (alveolar-arterial oxygen difference) for the SDH_{R_X} and SAH_{R_X} groups.

GROUP	FLOW	n	V_t	RR	$PaCO_2$	PaO_2	pH	RVP (mmHg)	A-aDO_2 (mmHg)
			(------------------% of pre - insult value			---------)			
SDH_{RX}	5	6	130±29	85±6	92±2*	83±7*	7.34±0.01	18±2	62±8*
SAH_{RX}	5	8	119±9	90±9	85±4*	97±3	7.37±0.01	17±2	46±7
SDH_{RX}	6	6	107±7	104±11	90±2+	86±8	7.35±0.01	16±1+	61±10
SAH_{RX}	6	8	109±10	100±7	91±3	92±4	7.36±0.01	16±1*	48±9
SDH_{RX}	7	6	109±9	101±9	91±3	87±6	7.36±0.01	17±2*	58±7*
SAH_{RX}	7	8	95±7	102±7	91±2	93±5	7.35±0.01	15±1*	55±10
SDH_{RX}	8	6	105±6	109±14	86±3*	89±5	7.36±0.01	19±2	59±7*
SAH_{RX}	8	7	100±10	102±10	85±2+	94±6	7.38±0.01	17±2	49±9
SDH_{RX}	9	6	118±10*	112±12	84±4+	84±4+	7.36±0.01	19±2	65±4+
SAH_{RX}	9	7	114±16	98±13	78±4*	92±7	7.41±0.02	16±2	55±10*
SDH_{RX}	10	6	117±9*	116±12	79±4+	88±4*	7.38±0.01*	19±2	64±4+
SAH_{RX}	10	6	103±8	106±10	75±3+	94±6	7.38±0.02	17±2	56±9
SDH_{RX}	11	6	116±10*	129±17	83±4+	86±7	7.38±0.01	21±2	64±7+
SAH_{RX}	11	6	108±15	114±12	79±3*	97±5	7.38±0.02	21±2	52±8

Table 28: Post-Insult. V_t, RR, $PaCO_2$ and PaO_2 as % of control, and pH, RVP and A-aDO_2 for CBF determinations 5 - 11. (*-$p<0.05$, +-$p<0.01$.).

GROUP	FLOW	n	MaBP mmHg	HR beats/minute	ICP mmHg	CPP mmHg	rCBF ml/100g/min	CVR Index	VC mm
R_X Alone	1	3	81±3	178±3		70±5	41±2	1.71±0.10	
	2	3	91±9	185±3		81±10	50±3	1.63±0.19	
	3	3	95±15	192±4		84±15	48±5	1.72±0.23	
	4	3	94±13	188±3	11±2	83±14	49±4	1.70±0.21	1.11±0.01
	MEAN		90±5	186±2		80±5	47±2	1.69±0.08	
SAH_{R_X}	1	8	98±7	198±7		84±7	58±4	1.53±0.20	
	2	8	93±6	199±7		80±6	54±5	1.53±0.16	
	3	8	100±7	202±6		87±7	56±4	1.62±0.20	
	4	8	102±8	201±7	13±1	87±8	53±5	1.71±0.20	1.16±0.06
	MEAN		98±3	199±3		85±3	55±2	1.60±0.09	
SDH_{R_X}	1	6	103±5	178±16		92±5	58±3	1.63±0.15	
	2	6	102±4	187±9		90±4	60±6	1.61±0.23	
	3	6	97±4	178±20		85±5	60±5	1.51±0.22	
	4	6	104±6	182±17	12±1	92±6	52±4	1.84±0.21	1.27±0.02
	MEAN	6	101±2	181±7		90±2	58±2	1.65±0.10	

Table 29: Pre- Insult. MaBP, HR, ICP, CPP, rCBF, CVR and VC (vessel caliber) for the R_X alone, SAH_{R_X} and SDH_{R_X} groups.

GROUP	FLOW	n	MaBP mmHg	HR beats/minute	ICP mmHg	CPP mmHg	rCBF % of pre-insult flow	CVR Index	VC % of pre-insult diameter
R_X Alone	5	3	96±10	190±8	10±2	86±11	95±4	1.93±0.23^{+}	
SAH$_{R_X}$	5	8	74±9^{+}	188±7	12±4	63±8^{+}	44±6^{+}	2.98±0.19^{+}	
SDH$_{R_X}$	5	6	81±4*	151±20*	9±5	72±3	44±7^{+}	3.11±0.30^{+}	
R_X Alone	6	3	74±3	205±10	14±6	60±8	82±6	1.56±0.23	102±4
SAH$_{R_X}$	6	8	75±6^{+}	212±8	11±4	62±7^{+}	56±4^{+}	2.34±0.32	68±4^{+}
SDH$_{R_X}$	6	6	85±3^{+}	193±15	13±3	72±5*	62±4^{+}	2.04±0.10	76±5^{+}
R_X Alone	7	3	79±6	202±7	17±4	62±10*	91±9	1.48±0.31	
SAH$_{R_X}$	7	8	76±6^{+}	201±10	10±2	65±7^{+}	58±6^{+}	2.23±0.35	
SDH$_{R_X}$	7	6	84±4*	183±15	14±4	70±6	71±3^{+}	1.73±0.12	
R_X Alone	8	3	76±3	205±3^{+}	14±2	62±5	82±9	1.65±0.24	
SAH$_{R_X}$	8	7	78±8^{+}	216±12	17±4	61±7^{+}	55±7^{+}	2.10±0.20	
SDH$_{R_X}$	8	6	82±4*	197±14	19±5	63±6	67±6^{+}	1.69±0.18	
R_X Alone	9	3	79±6	220±8	17±5	62±8	86±7	1.57±0.31	
SAH$_{R_X}$	9	7	74±8^{+}	207±20	11±3	62±6^{+}	51±6^{+}	2.34±0.24	
SDH$_{R_X}$	9	6	84±4*	205±14	23±3	61±5^{+}	65±4^{+}	1.67±0.13	
R_X Alone	10	3	74±5	218±11	17±6	56±11*	80±8	1.58±0.44	103±1
SAH$_{R_X}$	10	6	77±6^{+}	224±11	9±1	69±7*	50±6^{+}	2.53±0.30*	80±7*
SDH$_{R_X}$	10	6	83±3*	209±15	21±6	62±6*	69±3^{+}	1.59±0.16	90±4
R_X Alone	11	3	81±10	202±7	15±5	66±15	76±5*	1.87±0.48	101±2
SAH$_{R_X}$	11	6	94±9	220±14	5±3	91±12	58±6^{+}	3.19±0.36^{+}	86±7
SDH$_{R_X}$	11	6	93±5	211±16	19±5	74±4	67±4^{+}	2.03±0.25	92±4

Table 30: Post-Insult. MaBP, HR, ICP, CPP, rCBF (% of control), CVR and VC (vessel caliber - % of control) for CBF determinations 5 - 11. (*-$p<0.05$, +-$p<0.01$).

GROUP	FLOW	n	V_t ml	RR breaths/minute	$PaCO_2$ mmHg	PaO_2 mmHg	pH	RVP mmHg	A-aDO_2 (mmHg)
R_X Alone	1	3	17±3	37±5	46±4	117±4	7.32±0.04	25±2	54±11
	2	3	17±3	37±4	47±3	117±4	7.31±0.04	26±3	53±17
	3	3	17±3	36±2	45±2	112±6	7.33±0.03	25±2	60±11
	4	3	18±3	39±4	45±2	109±4	7.32±0.03	22±2	63±13
	MEAN		17±1	37±2	46±1	114±2	7.32±0.01	25±1	58±2
SAH_{RX}	1	8	19±1	35±2	42±2	113±2	7.34±0.02	22±1	36±3
	2	8	20±2	37±2	43±1	116±3	7.33±0.03	23±1	32±4
	3	8	22±2	38±2	41±1	114±3	7.35±0.02	22±1	39±4
	4	8	21±1	38±2	40±1	115±3	7.35±0.01	18±1	3 ±4
	MEAN		20±1	37±1	42±1	115±1	7.34±0.01	21±1	36±2
SDH_{RX}	1	6	20±2	31±2	40±1	114±3	7.34±0.01	23±1	39±2
	2	6	22±3	31±2	40±1	115±3	7.35±0.01	23±1	39±3
	3	6	21±2	32±3	40±1	112±4	7.34±0.01	23±1	40±4
	4	6	20±2	31±3	40±1	114±3	7.35±0.01	23±2	39±3
	MEAN		21±1	31±1	40±0	113±2	7.34±0.00	23±1	39±0

Table 31: Pre-Insult. V_t (tidal volume), RR (respiratory rate), $PaCO_2$, PaO_2, pH, RVH (right ventricular pressure) and A-aDO_2 (alveolar-arterial oxygen difference) for the R_X alone, SAH_{R_X} and SDH_{R_X} groups.

GROUP	FLOW	n	V_t	RR	$PaCO_2$	PaO_2	pH	RVP (mmHg)	$A\text{-}aDO_2$ (mmHg)
			(-------------------	% of pre - insult	value --------------	)			
R_X Alone	5	3	109±6	100±5	100±4	97±1	7.33±0.02	24±0	62±10
SAH_{R_X}	5	8	119±9	90±9	85±4*	97±3	7.37±0.01	17±2	46±7
SDH_{R_X}	5	6	130±29	85±6	92±2*	83±7*	7.34±0.01	18±2	62±8*
R_X Alone	6	8	100±7	108±4	90±4	93±2	7.33±0.02	16±1	72±9
SAH_{R_X}	6	8	109±10	100±7	91±3	92±4	7.36±0.01	16±1*	48±9
SDH_{R_X}	6	6	107±7	104±11	90±2+	86±8	7.35±0.01	16±1+	61±10
R_X Alone	7	3	99±16	91±1	90±5	94±5	7.33±0.02	17±2	70±16
SAH_{R_X}	7	8	95±7	102±7	91±2	93±5	7.35±0.01	15±1*	55±10
SDH_{R_X}	7	6	109±9	101±9	91±3	87±6	7.36± 0.01	17±2*	58±7*
R_X Alone	8	3	111±14	93±2	88±5	97±8	7.33±0.01	19±1	68±10
SAH_{R_X}	8	7	100±10	102±10	85±2+	94±6	7.38±0.01	17±2	49±9
SDH_{R_X}	8	6	105±6	109±14	86±3*	89±5	7.36±0.01	19±2	59±7*
R_X Alone	9	3	134±23	113±7	84±5	92±6	7.34±0.01	19±3	75±14
SAH_{R_X}	9	7	114±16	98±13	78±4*	92±7	7.41±0.02	16±2	55±10*
SDH_{R_X}	9	6	118±10*	112±12	84±4+	84±4+	7.36±0.01	19±2	65±4+
R_X Alone	10	3	125±23	113±12	81±4	91±6	7.34±0.01	20±1	79±12
SAH_{R_X}	10	6	103±8	106±10	75±3+	94±6	7.38±0.02	17±2	56±9
SDH_{R_X}	10	6	117±9*	116±12	79±4+	88±4*	7.38±0.01*	19±2	64±4+
R_X Alone	11	3	132±19	103±3	84±6	85±6	7.32±0.02	26±3	84±15*
SAH_{R_X}	11	6	108±15	114±12	79±3*	97±5	7.38±0.02	21±2	52±8
SDH_{R_X}	11	6	116±10*	129±17	83±4+	86±7	7.38±0.01	21±2	64±7+

Table 32: Post-Insult. V_t, RR, $PaCO_2$ and PaO_2 as % of control, and pH, RVP and $A\text{-}aDO_2$ for CBF determinations 5 - 11. (*-$p<0.05$, +-$p<0.01$).

GROUP	n	MEAN GRADE 5 HOURS	MEAN GRADE 20 HOURS
SAH	5	4.0	5.0
ARTIFICIAL CSF	5	1.4	1.0
SAH$_{Rx}$	8	4.3	4.9
SDH$_{Rx}$	6	1.9	1.7
Rx alone	3	2.2	5.0

Table 33: Neurological grade at 5 hours and 20 hours post-insult for the SAH$_{RX}$, SDH$_{RX}$, R$_X$ alone, 1.67 ml/kg SAH and Artificial CSF groups.

GROUP	FRESH WET BRAIN WEIGHT (gm)	$\frac{\text{BRAIN WEIGHT (gm)}}{\text{BODY WEIGHT (kg)}}$	FORMALDEHYDE BRAIN WEIGHT GAIN (gm)
SAH_{Rx}	62.4±2.0 (7)	20.2±0.9 (7)	6.8 (3)
SDH_{Rx}	61.8±2.0 (6)	20.7±1.5 (6)	7.3 (3)
Rx alone	60.1±0.6 (2)	26.8±0.9 (2)	6.6 (2)
SAH	61.7±2.3 (2)	19.9±0.1 (2)	2.2 (1)
Artificial CSF	60.6 (1)	27.5 (1)	3.5 (1)

Table 34: Mean fresh brain weight, brain weight/body weight and formaldehyde brain weight gain for the SAH_{RX}, SDH_{RX}, R_X alone, 1.67 ml/kg SAH and artificial CSF groups.

GROUP	IDICA	MCA	PPA	DPA
SAH_{Rx}	-	2	3	3
Rx alone	1	1	1	-

Table 35: Degree of vasoconstriction of cerebral vessels at E. M. for the SAH_{RX} and R_X alone groups. (IDICA - intradural internal carotid artery, MCA - middle cerebral artery, PPA - proximal pericallosal artery and DPA - distal pericallosal artery).